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The Second Blackader Lecture

ON

SOME ASPECTS OF VIRUS INFECTION, WITH SPECIAL REFERENCE TO VIRUS DISEASES OF CHILDHOOD*

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I DEEPLY appreciate the honour of having been invited to deliver this, the second of the Blackader lectures. I regard it not in any personal way but as a gratifying token of interest in that active field of medical research—the study of virus diseases. Indeed, I feel totally unworthy of the task which has been assigned to me, for these lectures were established in honour of Dr. A. D. Blackader during his lifetime, and, no matter to what subject they may be devoted, they are primarily a tribute to the personality and life-work of that distinguished physician and pioneer in pædiatrics in this continent.

INTRODUCTION

As our knowledge of the etiological agents of infectious disease has grown, the meaning of the term "virus" has been gradually changing. Over seventy years ago it signified, in a vague and indefinite way, a poisonous substance capable of engendering disease. The demonstration that many diseases of man and animals are due to infections with bacteria, spirochaetes, fungi, and protozoa restricted the meaning of the term to those transmissible causal agents of disease which could not be demonstrated microscopically or cultivated on the lifeless media of the bacteriological laboratory. These agents were found to be capable of traversing filters which retained bacteria, and

these bacteriologically sterile, but infective, filtrates revealed no organisms under the highest power of the microscope; hence the use of the qualifying adjectives "filterable" and "ultra-microscopic". More recently, since it has become recognized that some viruses are not altogether ultra-microscopic in size, and that some may pass through filters only with great difficulty, the tendency is to use the term "virus" without such qualifications.

Virus diseases not only affect man and animals but are also common in plants and insects, but with these we are not at present concerned. The viruses possess certain characters which serve to distinguish them as a group from the bacteria. The most important of these are size, failure to grow on lifeless culture media, and the production, by most of them, of characteristic intracellular changes.

Size.—Our knowledge of the approximate size of many viruses has been largely due to the development by Elford² of special membranes known as "gradocol membranes". These are collodion membranes which are prepared by a special technique which results in very thin membranes of remarkable uniformity of pore size and of average pore diameters ranging from 3μ to 10μ .* The average pore diameters of such membranes may readily be calculated, and

$$* \mu (\text{micron}) = \frac{1}{1,000} \text{ of a millimetre}$$

$$\mu\mu (\text{millimicron}) = \frac{1}{1,000,000} \text{ of a millimetre}$$

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by filtering a virus suspension through a graded series of such membranes, and determining the critical pore size for its retention, the probable size of the virus is arrived at. Virus sizes determined by this method show a close agreement with those determined by other methods such as ultra-violet light photomicrography for the larger viruses, and ultra-centrifugalization for the smaller. In Table 1 the sizes of some of them are given.

TABLE I

	Size
* <i>Oxyhæmoglobin</i>	3-5 $\mu\mu$
* Foot and Mouth Disease Virus .	8-12 $\mu\mu$
* Bacteriophage (smallest type) .	8-12 $\mu\mu$
* Yellow Fever Virus	8-15 $\mu\mu$
* Encephalitis (St. Louis) Virus	22-33 $\mu\mu$
Poliomyelitis	25-50 $\mu\mu$
* Fowl Plague Virus	60-90 $\mu\mu$
* Herpes Virus	100-150 $\mu\mu$
* Vaccinia Virus	125-175 $\mu\mu$
Green light—wave length	500-560 $\mu\mu$
<i>Staphylococcus</i>	800-1200 $\mu\mu$

* Size determined by filtration through gradocol membranes.

One feature of this Table is the considerable range of size among the viruses. Another is the minute size of the smallest. It is noteworthy that the smallest viruses are little more than twice the size of particles of hæmoglobin.

Although the smaller viruses are of an intangible nature and demonstrable only through the specific lesions that they produce in the infected animal some of the larger viruses can be demonstrated visually. By resorting to dark-field illumination some, for example vaccine virus, may be rendered visible as minute imperfectly resolved specks, and by employing a quartz system of lenses, ultra-violet illumination, and a photographic plate, a resolved image may be obtained.

Cultivation.—The second distinguishing feature of the viruses, the failure which so far has attended attempts to grow them on lifeless media such as are suitable for the cultivation of the bacteria, has a very important consequence. It means that the laboratory investigator of virus diseases is entirely dependent on experimental animals or tissue culture for the culture of a virus. Some of the viruses pathogenic for man, such as those of poliomyelitis, herpes simplex, encephalitis of the St. Louis type, and yellow fever, are transmissible to animals. They do not show a strict

species specificity and can therefore be propagated and investigated in the laboratory. There are good reasons for believing that some other diseases of man, such as chicken-pox, herpes zoster, and type A epidemic encephalitis, are virus diseases although their transmission to animals has never been convincingly demonstrated.

At this point it might be well to indicate just what is required in the way of experimental evidence before a given morbid condition can be attributed to a virus. The demonstration that bacteriologically sterile filtrates of tissue involved in the disease process are capable of inducing the disease in animals, and that the disease can be transmitted from animal to animal in this way by means of filtrates is good evidence, and this is further strengthened if we can show that the serum of recovered human cases of the disease is capable of neutralizing and rendering inactive the infective filtrates, while normal human serum has no such property. Sometimes the disease transmitted to the animal by the filtrate does not yield the same pathological and clinical picture as the human disease—small-pox virus produces only a transient local lesion in the skin of the rabbit and the virus of herpes simplex in the rabbit may lose its benign dermatotropic qualities and become virulently neurotropic. Nevertheless, although the clinical and pathological pictures of the human and experimentally induced animal condition may not be identical, their etiological identity, *i.e.*, their causation by the same virus, is proved if sera of human cases convalescent from the disease can be shown to possess specific neutralizing properties for the virus.

Inclusion bodies.—The third distinguishing feature of animal viruses which I have mentioned is the production of characteristic intracellular changes. In addition to the ability to produce hypertrophy or necrosis of a cell, many viruses produce peculiar changes in the cell, either in the cytoplasm or the nucleus. Bodies, known as inclusion bodies, which are readily demonstrable by certain combinations of stains, make their appearance in the cell exposed to the virus. The intranuclear type of inclusion body (Fig. 1) is produced by many viruses, herpes, chicken-pox, virus III, salivary gland virus of guinea-pigs, Borna disease, and others. Cytoplasmic inclusions (Fig. 2) are

found, for example, in vaccinia, fowl pox, rabies. In the case of rabies and small-pox these bodies are so characteristic, as to be of diagnostic importance. In some cases inclusion bodies are certainly degenerative changes brought about by the action of the virus; in others they are actually colonies of the virus; in still other cases their nature is not known with certainty.

Inclusion bodies in children.—Although the production of characteristic inclusion bodies is

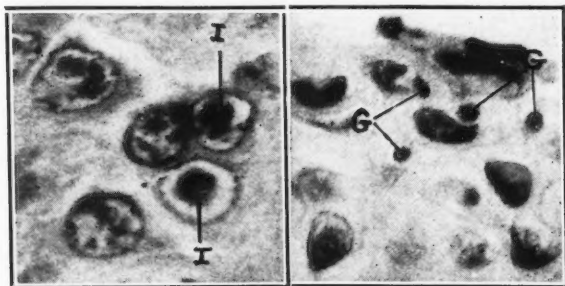


FIG. 1

FIG. 2

FIG. 1.—Intranuclear inclusion bodies (I) in brain of rabbit dying of herpetic encephalitis. (x 1,000).

FIG. 2.—Cytoplasmic inclusion bodies (Guarnieri bodies—G) in corneal cells of rabbit. The cornea was inoculated with small-pox vesicle fluid. (x 1,000).

a striking effect of the action of many viruses, they may be found in various animal species without clinical signs of a related virus infection or even unrelated to any known virus infection. In spite of repeated attempts by numerous investigators, intranuclear alterations of this kind have never been produced by agents other than viruses. The finding of intranuclear inclusions therefore raises the suspicion of virus action, and in this event some authors hold that the presence of a virus should be assumed unless it is possible to prove experimentally that a virus is absent. Numerous observers have reported the finding of inclusion bodies in children and infants, and these provide an interesting but difficult problem. A recent survey by Farber and Wolbach⁵ of the submaxillary glands of infants coming to autopsy revealed the presence of inclusion bodies in 12 per cent of 183 infants. Clinical and pathological studies revealed no relationship between the presence of these bodies and any disease changes or group of symptoms. Inclusion bodies have also been found in the lungs of children. Unlike the submaxillary gland inclusions, a considerable percentage of these lung inclusions have been related to a specific infection, and this specific infection is

whooping-cough. McCordock and Smith¹⁰ have recently described the finding of intranuclear inclusion bodies in 18 out of a series of 40 autopsies on children who had died of pertussis. Their survey was carried out in search of evidence that a virus might play an essential part in the production of interstitial pneumonia—a lesion found in nearly all fatal cases of whooping-cough. There are three human diseases in which this type of pneumonia may occur as a complication. One is measles, an accepted virus disease; another is influenza, and there are strong reasons for believing that in this infection a virus plays a part at least as important as Pfeiffer's bacillus; the third is whooping-cough. Now whooping-cough is unquestionably due to infection with the Bordet-Gengou bacillus, and there seem to be no reasons for assuming that a virus plays any part in the uncomplicated disease. However, it is not impossible that an unknown virus may contribute to the interstitial pneumonia of pertussis.

IMMUNITY

One feature of most virus infections that has often been commented upon is the lasting nature of the immunity which is produced. Attacks of small-pox, chicken-pox, measles, mumps, poliomyelitis and yellow fever confer an immunity which is life-long in the vast majority of cases. Little is known of the actual nature of this immunity; of what happens when the virus is introduced into the tissues of an immune animal. It is true that immune bodies against a virus can be demonstrated in the blood of an animal immune to that virus, but the action of these immune bodies on the virus is a complex and incompletely elucidated affair. In the case of some viruses, at least, it may readily be proved that in neutral mixtures of immune serum and virus which will not produce a lesion or clinical infection the virus is not dead but merely masked by the presence of the serum. Vaccinia or herpes immune sera render the virus an easy prey for leucocytes, and in some other virus diseases phagocytosis is probably of great importance in immunity.

In connection with the action of immune serum on a virus there is a very important fact which requires emphasis. An immune serum, no matter how potent, will not neutralize a

virus after the virus has come in contact with the cell. Once the virus has parasitized the cell it is protected from immune serum which can then only limit the spread of the virus from the cell. This can be shown by exposing living cells for a brief period to a virus and then growing these cells in immune serum. In spite of their environment the cells develop specific virus lesions or inclusion bodies.¹⁷ Another type of experiment which demonstrates this phenomenon is illustrated in Fig. 3.

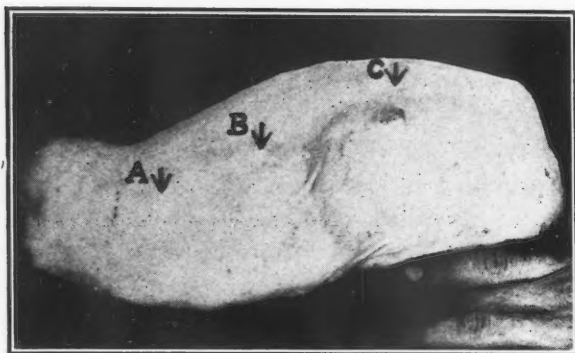


FIG. 3

- A. 0.2 c.c. antivaccinia serum + (30 minutes later) 0.2 c.c. vaccine virus.
- B. 0.2 c.c. vaccine virus + (30 seconds later) 0.2 c.c. antivaccinia serum.
- C. 0.2 c.c. vaccine virus + (1½ hours later) 0.2 c.c. antivaccinia serum.

The vaccine virus used was a washed suspension of vaccinia elementary bodies, representing 1,000 minimal infective doses. Serum and virus were injected intradermally, all three injections of virus being made at the same time. Photographed on 5th day after inoculation. The development of an intradermal reaction at C shows the failure of serum to prevent a local lesion when injected after the virus.

Some virus diseases of man are highly contagious, and exposure of those not previously attacked is followed almost inevitably by development of the disease. But in some other virus diseases there are very good grounds for believing that subclinical immunization may occur, as it does in diphtheria and other bacterial diseases, and that atypical cases and healthy carriers may play an important part in the spread of the virus. In poliomyelitis the specific virus has been demonstrated in the nasal secretions of healthy individuals, and Aycock and Kramer and also Brodie¹⁶ have reported the presence of neutralizing antibodies for poliomyelitis virus in a large percentage of normal persons with no history of poliomyelitis. In certain areas of west Africa clinical cases of yellow fever are infrequent, and it has been shown that in these areas a high proportion of the children have specific neutralizing anti-

bodies in their blood. There is every reason to believe that these neutralizing antibodies owe their origin to subclinical infection at an early age. Stocks has shown that the natural history of the prevalent virus diseases, measles, German measles, and chicken-pox is closely analogous to that of diphtheria or scarlet fever.¹⁷ His careful analysis of the relevant data has shown that the morbidity figures for these diseases cannot be explained except by the assumption that specific immunization can occur in the absence of diagnosed disease. Concerning poliomyelitis Stocks has calculated that for every paralytic case of the disease one hundred individuals become immune, and Aycock¹⁶ has given a similar estimate.

SMALL-POX AND VACCINIA

In a disease such as small-pox, on the other hand, subclinical immunization by contact with a case rarely, if ever, occurs, if one excepts that mild, yet troublesome, form known as variola minor. In populations in which a proportion of the child population is vaccinated, small-pox is not regarded as a disease of children, but in the absence of vaccination a higher incidence and mortality in these age-groups is to be expected. When small-pox gradually came into prominence in Great Britain in the Stuart period, and for a long time afterwards, this disease only incidentally affected adults; it affected and produced its greatest fatality in infants and children. In the years 1783 to 1800 a severe epidemic of small-pox raged in Glasgow, and it is noteworthy that 90 per cent of the deaths in the epidemic occurred in children under five years of age.

For nearly forty years the skin of a healthy calf has been the standard culture medium for the production of vaccine virus. Recently two methods of growing the virus in the laboratory have been developed, and the virus thus grown has been employed successfully for vaccination. One of these, developed by Goodpasture,⁶ is to grow the virus on the chorio-allantoic membrane of 10 to 12 day-old chick embryos. The other is a tissue-culture method and has been developed by Rivers and Ward.¹¹ The virus is implanted in flasks containing Tyrode's solution and minced chick embryo, and grown for 4 to 5 days. Children have been successfully vaccinated with virus cultivated in this way, and subsequent tests have shown that they were

completely refractory to inoculation with calf virus. Neither fever nor constitutional disturbance was produced in children vaccinated with this culture virus.

In 1906 Paschen demonstrated by a special staining method extremely minute bodies in the vesicle fluid of small-pox and vaccinia. He considered that these bodies represented the virus, but this view received little acceptance. The prevailing view was that they were either non-specific particles or artefacts. The study of these Paschen, or elementary, bodies was taken up by Ledingham who found that in the case of vaccinia it was possible to separate them, and

tary bodies are identical with those produced by the crude virus preparation, and the capacity of the suspensions to produce lesions is specifically neutralized by vaccinia immune serum. (5) The early or sensitivity reaction found in the revaccination of previously vaccinated individuals can be elicited as readily by killed suspensions of vaccinia elementary bodies as by vaccine virus as used for human vaccination.

It is worthy of note that antivaccinia serum prepared by hyperimmunization of the rabbit

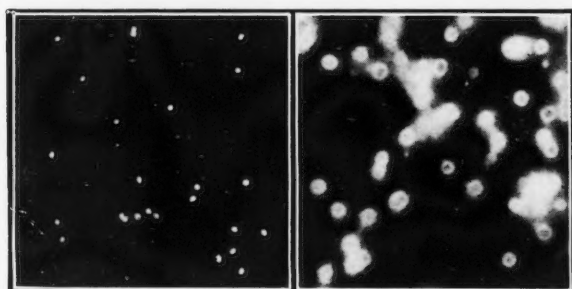


FIG. 4

FIG. 5

FIG. 4.—Vaccinia elementary bodies (Zeiss cardoid condenser and No. HI. 60 objective; Ilford micro No. 1 screen; $\times 2,000$). The size of the bodies is exaggerated on account of imperfect resolution.

FIG. 5.—*Staphylococcus aureus* photographed under the same conditions. ($\times 2,000$).

he showed by means of the hanging drop agglutination method that suspensions of these bodies were specifically clumped by immune serum. It has since been shown that true agglutination of these bodies may be brought about by the addition of vaccinia immune serum, and it is now possible to prepare pure suspensions of them on a large scale (Fig. 4), sufficiently dense to permit not only macroscopic agglutination tests but also absorption tests being carried out. There is every reason to believe that these bodies represent the virus of vaccinia (or of variola when derived from a case of this disease). Briefly, the evidence is as follows. (1) The virus is inseparable from them, whether we employ fractional centrifugation or filtration in an attempt to separate them. (2) They increase enormously in numbers in the developing vaccinal lesion, and in tissue cultures of vaccine virus. (3) They are specifically agglutinated by immune serum (Fig. 6), and also fix complement with immune serum. (4) The lesions produced by pure, repeatedly washed suspensions of these elemen-

VACCINIA IMMUNE RABBIT SERUM					NORMAL RABBIT SERUM			
DILUTED 1 IN					DILUTED 1 IN			
50	100	200	400	800	50	100	200	400

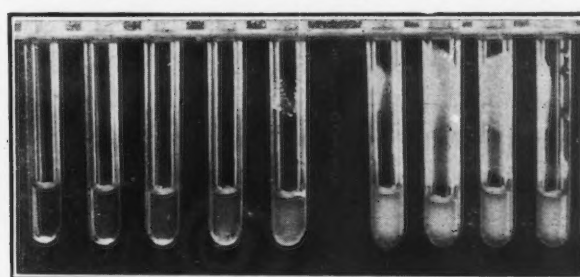


FIG. 6.—Agglutination of a pure, thrice-washed, suspension of vaccinia elementary bodies; test incubated 16 hours at 56°C .

with vaccinia elementary bodies not only neutralizes small-pox elementary bodies but agglutinates them, fixes complement with them, and precipitates the specific precipitable substance which is a product of the elementary body. This specific precipitable substance is of diagnostic importance in small-pox. It is present in the vesicle fluid and scabs of this disease, and a suitable prepared extract of either of these morbid products containing the specific precipitable substance yields both a precipitin reaction and a complement-fixation reaction with antivaccinia serum obtained from the rabbit. The complement-fixation reaction is the more sensitive of the two reactions; both are of very definite value in cases which present difficulty in diagnosis.

Vaccine virus produces effective immunity in a shorter period after inoculation than does smallpox virus after exposure. Hence it is usually possible to protect an individual or to modify the attack if vaccination is carried out within a few days of exposure, and this method is the one usually relied on. Here, however, would seem to be a definite field for specific serum therapy. Immune serum is of no value once the disease is established, but has been suc-

cessfully employed as a temporary prophylaxis. Sometimes vaccination performed immediately after exposure may fail to protect, as a recent case which occurred in the Dominion shows. An undertaker handled the body in a fatal case of small-pox, and then it was discovered that he had no evidence of successful vaccination. He was vaccinated immediately, but became ill with small-pox in spite of a taking vaccination eight days after contact, and he died nine days later. On several occasions a small-pox outbreak in this Dominion has commenced with atypical and rapidly fatal cases which at the time were diagnosed as purpura or hæmorrhagic measles. Such a delay in diagnosis means that subsequent vaccination of contacts of the missed cases is too late to modify the disease. After vaccination the minute amount of virus introduced as seed probably requires a few days for multiplication before the antigenic stimulus becomes adequate. Serum provides an immediate supply of immune bodies, and I suggest that where there is a delay between contact with virulent small-pox and vaccination that immune serum or blood should be administered. To be effective the serum would have to be administered before the onset of the first symptoms and might well be preceded by an intradermal injection of vaccine virus (*vide* Fig. 3).

VARICELLA

The virus of chicken-pox presents an interesting contrast to vaccine virus in its strict species specificity. Susceptibles readily contract the disease on exposure to a case, but the disease has never been transmitted to an experimental animal. Even attempts to transmit the disease in man by dermal inoculation with vesicle fluid have not been uniformly successful. Aragao and, later, Paschen, demonstrated in the vesicle fluid of chicken-pox minute bodies similar in size to those of vaccinia and small-pox. The view that these bodies represent the virus of chicken-pox has been greatly strengthened by recent observations by Amies.¹ Amies harvested vesicle fluid from cases of chicken-pox directly into a saline-citrate mixture and, by a differential centrifugation technique similar to that employed by him for the isolation of small-pox elementary bodies, obtained pure suspensions of varicella elementary bodies. Hanging-drop agglutination tests were set up with these suspensions. The varicella elementary bodies were

observed to agglutinate in the presence of convalescent varicella serum. They did not agglutinate in normal sera from man, monkey or rabbit, nor in antiserum from animals hyperimmunized against vaccinia. More recently, Amies⁹ has obtained suspensions of herpes zoster elementary bodies, and has found that cross agglutination occurs between zoster and chicken-pox elementary bodies and zoster and chicken-pox convalescent sera. This observation supports the belief that these two viruses are related.

MEASLES

Measles is an outstanding example of a virus disease which can be completely controlled by immune serum therapy. The brilliant success which has attended efforts to control it in this way has been due to the efforts of physicians and health officers. At most, the laboratory investigator's contribution has been information of a general nature concerning the properties of immune serum in other virus diseases. Measles shows a marked species specificity, and the work of Blake and Trask, in which they transmitted a condition resembling measles to monkeys by means of filtrates of upper respiratory tract washings from cases of measles, has been the only convincing evidence that the virus may be transmitted to an animal. However, the great infectivity of measles, and the degree of certainty with which the disease will attack an exposed susceptible, have compensated for the lack of a suitable experimental animal, and made possible the conduct and interpretation of experiments in children on the value of specific serum treatment and prophylaxis.

I do not intend to recount the history of the serum prophylaxis of measles which was proposed by Nicolle and Conseil in 1918, but merely to summarize its principles and method.* An attack of measles produces a very high degree of immunity and this immunity is associated with the presence of immune bodies in the serum of the immune individual. The immune serum or blood, if administered to a susceptible individual after he has been exposed to measles' infection may either prevent or modify the attack. If administered within five days of contact complete protection is secured, but the immunity is purely passive and fades after two to four weeks, after which the

* For references see Topley.¹⁷

child again becomes susceptible. Given between the seventh and the ninth day the serum does not prevent an attack, but the attack is very mild. This modified and benign attack confers a lasting immunity. If given between the fifth and seventh days the serum either gives complete protection with transient immunity or a mild attack with permanent immunity, and to some extent the outcome depends on the potency and amount of serum administered. The fatality rate of measles shows a strict correlation with age. If the attack be postponed to five years of age the risk of death is trivial, but in the first two years of life the fatality rate may be quite high. The indications therefore are as follows. If the exposed child is under five years of age, or if older, but ill with some other disease, prevent the attack by prompt administration of serum; 40 per cent of protection is lost if inoculation is delayed beyond the fifth day of exposure. If the child is five or over and healthy, aim at attenuation and permanent immunity by delaying the administration of serum.

MUMPS

The virus nature of mumps was definitely indicated by the work of Gordon and of Wollstein and recently has been established beyond question by Johnson and Goodpasture.⁸ The latter injected specimens of saliva from cases of mumps directly into Stensen's duct in the monkey. Specimens obtained within twenty-four hours of the first noticeable swelling of the parotid gave rise to an acute non-suppurative parotitis analogous to mumps, which was accompanied by slight fever and leucopenia, with a true monocytosis and a relative lymphocytosis. The virus was transferred through seven generations in monkeys and was shown to be filterable and relatively resistant to glycerol. A preliminary attempt was made to determine whether serum from recently recovered cases of mumps contains a neutralizing antibody for this virus. Some inhibiting effect was demonstrated, but, as Johnson and Goodpasture point out, much more extensive investigation of this problem is required. Since Hess in 1915 employed mumps convalescent serum for prophylaxis a number of authors have reported on its efficacy. While most agree that it will afford definite protection, investigation of its value has not been sufficiently extensive

to permit the statement that it is as efficient as measles convalescent serum. Theoretically, the long incubation period of mumps ought to facilitate such specific prophylaxis when circumstances make it desirable.

POLIOMYELITIS

Poliomyelitis is a subject to which I refer with some diffidence, and I may disappoint some of you by refraining from any dogmatic pronouncement on the value of immune serum or the question of whether this disease in man is primarily one of the central nervous system or a systemic infection with secondary invasion of the central nervous system. I feel that our knowledge of this disease and of the causal virus is not yet sufficient to permit a judgment concerning these vital questions. I shall deal with the nature of the disease in man first, since this has such an important bearing on the question of the value of immune serum therapy.

Draper, possibly more than anyone else, has been responsible for the entrenchment in the minds of the medical profession of the conception of poliomyelitis as a systemic or general infection with a subsequent invasion of the central nervous system. Draper's book on poliomyelitis was, according to its author, "designed to develop the idea that acute poliomyelitis is a general infectious disease, in the course of which paralysis is but an accidental and incidental occurrence".

Fairbrother and Hurst in 1930 demonstrated experimentally that poliomyelitis in the monkey spreads *via* the axis cylinders, and further experimental work has confirmed this. Recently Faber³ has reconsidered the pathology and symptomatology of poliomyelitis in man on this basis. According to the axonal hypothesis presented by him, the virus deposited on the olfactory mucous membrane may come in contact with the terminal filaments of the olfactory ganglion cells and penetrate them. Having done so it ascends along the axons of the olfactory nerves to the olfactory bulb. Its neural pathway lies through the hypothalamus, the thalamus, and mid-brain, where it produces lesions which give rise to those symptoms characteristic of the onset of poliomyelitis. The virus reaches the medulla from the hypothalamus, while from the lateral thalamus it spreads along the spino-thalamic tract to the posterior horn of the spinal cord, from whence

it passes to the dorsal root ganglia and to the anterior horn cells.

Faber does not forget those lesions that occur outside the central nervous system. He points out that, apart from cloudy swelling (probably a terminal lesion), the extra-nervous manifestation of this disease is a lymphoid hyperplasia, and explains this as a response to mobilization of lymphocytes to the central nervous system, where in the most heavily infected areas they produce wide collars of perivascular infiltration. He regards poliomyelitis as an infection solely of the central nervous system. From the olfactory nerves the virus travels by purely neural pathways until it may finally reach the anterior horn and produce the culminating paralysis. The signs and symptoms of the various stages of the disease are referred to infection of specific parts of the central nervous system. The progress of the virus may be delayed for a little at various points while it mobilizes in sufficient strength to invade the next section of the route, or, alternatively, it may find conditions unfavourable at any point in its path and die out, and recovery occurs without paralysis. Faber lays stress on the delay of the progress of the virus at one time or another. He states that the phenomenon of "halting", as he calls it, is detectable in nearly all typical cases in which infection is not fulminant and overwhelming, and that its significance and importance has been confused and insufficiently appreciated in the past.

I think that most laboratory workers will have little to say in criticism of the axonal hypothesis. It certainly seems to be true of experimental poliomyelitis in the monkey. Most criticism will come from clinical observers who are unable to reconcile certain aspects of the symptomatology with the idea that the nervous system alone is involved. Most laboratory work with poliomyelitis induced by neural or intracerebral inoculation of the monkey is artificial so far as the route of inoculation is concerned, but Schultz and Gebhardt¹² report that infection with the virus by the intranasal route can be brought about in 95 per cent of animals if intranasal washes with dilute acid buffer precede the instillation of virus. These authors¹⁴ have also shown that complete severance of both olfactory tracts with the electric cautery completely protected monkeys against infection by the nasal route. Faber and Gebhardt,⁴ infecting monkeys

in this way by the nasal route, and mapping out the progress of the virus by sacrificing some of the animals on successive days, have obtained evidence which completely supports the axonal theory as propounded by Faber.

It has been suggested that the axonal hypothesis is untenable, because the phenomena of immunity to poliomyelitis, particularly subclinical immunization, cannot be explained without accepting systemic infection. Faber regards subclinical infection which leads to immunity as a striking example of the phenomenon of "halting". He conjectures that in such a case the infection progresses no further than the olfactory cells or olfactory bulb. Now, the axonal hypothesis as propounded by Faber really involves two distinct ideas which require separation. One is axonal or nerve-fibre propagation of the virus in man following invasion of the olfactory hairs, and this is probably correct. The other is strict neurotropism of the virus. If we mean by strict neurotropism that the virus never gains access to other tissues we are on uncertain ground. The leucocytes, the mobilization of which is such a striking part of the pathological picture, are probably an important link in the development of immunity in the clinical case, and may transport virus out from the central nervous system, but in other cases the virus of poliomyelitis may possibly gain access to the blood stream or tissues in other ways.

If there is systemic infection or invasion by the virus it might be expected that the virus could be recovered from the blood stream. Numerous investigators have sought to demonstrate its presence in the blood of human cases but all results have been negative. Strict interpretation of these observations would be that the virus has never been encountered in sufficient amount in the blood of cases to permit of successful transfer to monkeys. They do not permit the categorical denial that the virus ever finds its way into the blood stream. Poliomyelitis virus has been found in the nasopharynx not only in paralytic cases but in abortive cases and healthy contacts. It is quite possible that the virus may gain access to the blood stream and yet be removed sufficiently rapidly to maintain such a low concentration as cannot be detected. Monkeys have been immunized to poliomyelitis, without the development of clinical symptoms, by intracutaneous

injection of the virus. On the other hand, spraying the nose and throat of monkeys with virus emulsion, if it does not cause poliomyelitis, does not appear to produce immunity, even when performed twice weekly for ten weeks. Yet the theory of latent immunization of man to poliomyelitis is based on the idea of the implantation of the virus in the respiratory tract.

If we look further afield in virus diseases we may encounter some facts which may make us hesitate to accept Faber's views concerning the strict confinement of poliomyelitis virus to the central nervous system in man. The virus of "louping ill"—a virus disease of sheep—is pathogenic for mice. Instilled into the noses of susceptible mice it invades the brain and blood stream, but when the cortical infection becomes established and symptoms appear it tends to disappear from the blood. In a horse dying of equine encephalomyelitis the virus is found only in the central nervous system, but previous to the onset of signs of infection it may be recovered in considerable quantities from the blood, and a similar phenomenon is manifested by some other "neurotropic" viruses.*

There is always a certain hazard in acclimatizing a virus to a new soil, and that is what has to be done in transmitting poliomyelitis virus from man to the monkey. Relatively few strains of poliomyelitis virus have been isolated and carried through a large series of monkeys.¹⁰ When poliomyelitis virus is transmitted from man to the monkey either adaptation of the virus occurs or it dies out after a few passages. "Although", as Amoss states, "there is no experimental disease which so clearly reflects in its clinical aspects the human analogue as does experimental poliomyelitis", there might be some justification in hesitating to accept the analogy as perfectly complete in every detail. It is not impossible that in man poliomyelitis virus may have some tendency to enter the blood stream or invade tissues without necessarily causing any symptoms referable thereto, but that this tendency is lost when the virus is established in the monkey. Mere access of the virus to the system in general, as opposed to manifest infection, would serve to explain the development of neutralizing antibody in individuals who have never shown clinical signs of infection. Much rests on whether the hypothesis of strict

neurotropism and axonal propagation of poliomyelitis is correct — the interpretation of early clinical manifestations and of the epidemiology of the disease, the explanation of subclinical immunization, and the problem of immune serum therapy. Faber's work constitutes a definite challenge to physicians, for in their hands rests the problem of examining the hypothesis critically in the light of clinical observation of the disease in man.

Only a proportion of clinical cases of poliomyelitis progress to paralysis. Since there is no way of foretelling whether a particular case in the early stage will do so or not if specific treatment is withheld, it is manifestly impossible to judge the value of the administration of immune serum in a particular case, and controls are therefore essential. The only adequately controlled observations on the value of immune serum are those of Kramer and Aycock and those reported by Park for the 1931 epidemic in New York.¹⁶ These reports certainly do not indicate that immune serum has any therapeutic value. On the other hand, we cannot overlook the conviction of competent and careful observers that poliomyelitis immune serum is of value when administered in the pre-paralytic stage. The experience in the outbreaks of poliomyelitis in Manitoba, Ontario and Quebec has been definitely in favour of serum treatment. Macnamara and Morgan went as far as to state that "if the patient has not improved within twenty hours there has been one reason only—insufficient dosage". The question of the value of immune serum in the early stages of poliomyelitis is an urgent problem. If serum is of no value the sooner the fact is definitely established the better, and all our efforts against this disease may be directed into other channels.

If we want to be thoroughly pessimistic about the use of immune serum in the treatment of poliomyelitis, we can agree to the argument that serum is useless, since the earliest clinical signs indicate entrenchment of the virus in the diencephalon, and that serum is powerless against the virus once it has gained access to the central nervous system. However, the phenomenon of "halting" in poliomyelitis would seem to indicate that the virus in man may be held up at certain barriers, presumably the synapses, and there might seem to be some reasonable hope of increasing the

* See Hurst⁷ for discussion and references.

resistance of these barriers by an adequate supply of immune bodies. Serum, even serum so potent that 1 c.c. was able to inactivate *in vitro* at least 25,000 minimal infective doses of poliomyelitis virus, is unable to appreciably affect the course of infection in monkeys if given later than the second day after infection by intranasal instillation of the virus (Schultz and Gebhardt¹³). If this applies to man it limits the field of usefulness of immune serum to prophylaxis. However, the disease in the monkey differs from that in man, in that the infection, once established, shows a much greater tendency to march its full course.

I feel that immune serum deserves a further trial, not only under circumstances whereby the observations can be completely controlled, but by the only route by which it can become immediately available, *i.e.*, intravenously. If the serum is to have any beneficial effect its action must begin immediately, and absorption after intramuscular injection is slow. Administered intrathecally, the serum cannot possibly reach the sites of infection (we are not dealing with a meningitis) and may be actually harmful because of the reactions set up. The serum should be of known capacity to neutralize the virus, and it is highly desirable that it should have been prepared in such a way that it is suitable for intravenous injection.

Flexner and Stewart proposed the use of convalescent serum for passive immunization of children in times of epidemic poliomyelitis. Park was instrumental in having this suggestion carried into effect, and Brebner gave parent's blood or convalescent serum to 1,200 leaving 2,400 untreated. Only 1 suspected case occurred in the treated group, while 21 cases developed among the untreated. Park suggests a dose of 50 c.c. of whole citrated blood. This would have to be repeated in three weeks, since the immunity is only passive.

One wonders if greater attention should not be directed to the route of infection. The generally accepted portal of entry is the nasopharynx, and the theory of axonal propagation of the virus specifically indicates the olfactory hairs, which are modified dendrites of the olfactory bulb. Faber points out the importance of the mucus overlying the olfactory hairs. If virus be implanted in this site the only effective immediate barrier to the neural entry of virus is the mucus and the resistance

of that portion of the cell membrane covering the olfactory hair. I have already mentioned that washing of the nasal cavities of monkeys with weak acid buffer solution greatly facilitates infection with the virus after intranasal instillation. Is it more than coincidence that in poliomyelitis it is the healthy rather than the sickly child which is attacked, and that the disease should have its maximum incidence in summer and early fall when catarrhal conditions of the upper respiratory tract are minimal?

Within the limits of this review it has been impossible to touch on many points of interest. For example, I have made no reference to the viruses of human or of swine influenza, or to the phenomena of the combined action of virus and bacterium. Immunity to viruses, in spite of its importance, has been dismissed with a brevity which the subject by no means merits. Omissions in this review do not signify that the matters involved are unimportant. The study of virus diseases is a rapidly expanding field, and even that portion of it which relates to virus diseases of children cannot be indicated adequately within the confines of this presentation.

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FRACTURES OF THE TALUS*

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IN civil practice fractures of the talus are somewhat rarely met with. They are generally the outcome of considerable violence, such as a fall from a height, and the more usual result of this is a fracture of the calcaneus. Montgomery, however, quotes Golebriwski as having seen 77 and Borchardt 12 within a few years. On the other hand, Roth speaks of having seen only 2 cases. Sawyer describes 3 cases seen by him, and Mowell states that "fractured astragalus without dislocation is a very common injury". Mercer described 2 cases and discussed the mechanism of the fracture. As one result of an airplane crash, the injury is comparatively common; Anderson referred to 78 such cases. Most surgeons will agree that the fracture is not at all common. Even when it does occur, it is apt to be overlooked. Thus Graham and Faulkner, in reviewing 10 cases seen between 1919 and 1929, and in whom astragalectomy had been performed, found that only 3 had been diagnosed within a month of injury, *viz.*, ten days, three weeks, and four weeks, respectively, after receipt of the injury. Confusion doubtless arises from interpretation of the phrase "fracture of the astragalus". Many cases show a comparatively trifling degree of crushing of the head or of the body of the bone. These are apt to elude detection until radiographed. On the other hand fracture of the bone with gross displacement produces a deformity so glaring that it could hardly be overlooked. It is this form that is much more rare.

Fracture may occur at any part of the bone. There may be crushing of the head or of the body, or the fracture may be through the neck. The break in the neck may be a mere crack unaccompanied by displacement, or one of the fragments may be dislocated. The anterior portion may be pushed upwards and forwards so

as to over-ride the posterior fragment, the navicular, or the cuboid. Forward displacement of the posterior fragment has been recorded in two cases, the separated portion coming to lie beneath the skin in front of the lateral malleolus. Backward displacement of the posterior fragment is much less rare. In this form of the lesion the body of the bone is forced backwards and is generally rotated, so that the articular surface of the talus looks upwards and medially, while the fractured surface looks towards the ground. Backward displacement without rotation is very rare, only two cases being on record.

ANATOMY

Attached to the talus we have the following ligaments: (a) the interosseous, occupying the sinus tarsi, and binding the talus to the calcaneus; (b) the posterior talo-fibular, passing from the fossa behind the articular facet at the lower end of the fibula almost horizontally to the posterior process of the talus and to the groove below the articular surface; (c) the deep portion of the deltoid, passing from the lower border of the medial malleolus to the medial side of the body of the talus "under the tail of the comma-shaped facet" and to the ridge running forwards to the neck.

Tendons in relation.—The flexor longus hallucis, clinging to the posterior aspect, between the medial and lateral parts of the posterior process of the bone. The tibialis posterior and flexor longus digitorum are in close proximity to the medial border of the posterior surface. The tendo Achillis, in the right-angled position of the foot, stands well away from the talus, but in forced dorsiflexion can come into actual contact with the posterior part of the articular surface. In this position, owing to the eversion of the heel which accompanies dorsiflexion at the ankle-joint, the tendo Achillis lies to the lateral side of the flexor longus hallucis tendon.

MECHANISM

Experiments.—A dissected limb was used for the first of these. It had been hardened in formalin, and in the course of dissection the tendo Achillis and the tendon of the flexor longus hallucis had been cut. Strong manual dorsiflexion at the ankle-joint was carried out, and this was later combined with strong manual eversion. The sequence of events observed was as follows. The normal movement of the talus

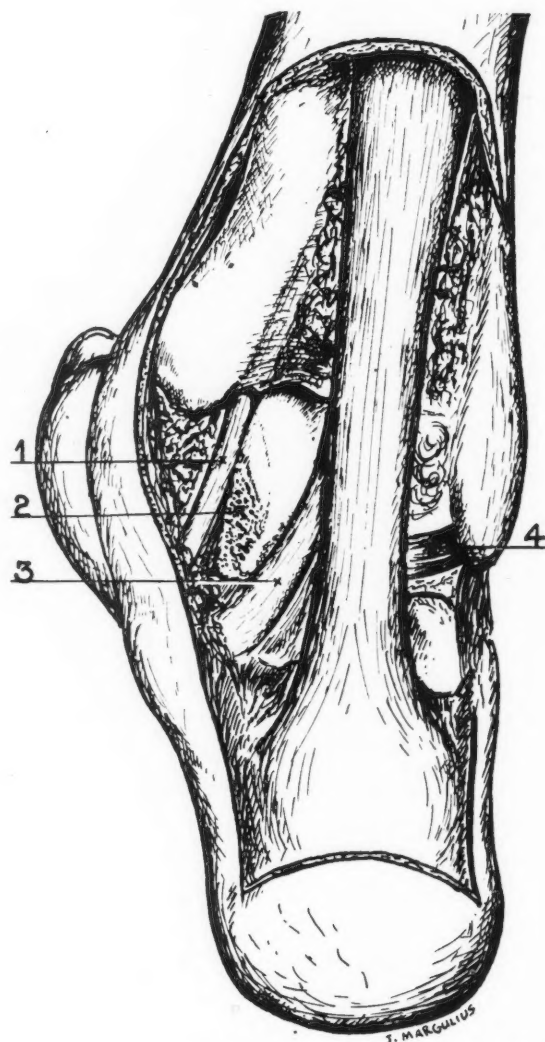
* An address given before the Winnipeg Medical Society, December, 1933.

under the tibia was passed through to the limit of dorsiflexion. At the end of this movement some eversion of the heel was observed. Next, still further forced dorsiflexion caused movement between the talus and the calcaneus, this movement accentuating considerably the degree of eversion. Further pressure in the direction of dorsiflexion and eversion brought about rupture of the posterior ligament of the ankle-joint, the posterior tibio-calcanean fibres of the deltoid ligament, and the medial fibres of the interosseous ligament successively. It was noted that the movement of forced dorsiflexion is accompanied by a pronounced measure of eversion of the heel, that the tendon of the flexor longus hallucis bears strongly in a lateral direction, and that the posterior talo-fibular fibres remained intact throughout.

A second observation was made on a limb amputated through the leg about the junction of upper and middle thirds for senile gangrene. This was unfixed and therefore flexible. An incision was made through the neck of the talus close to the body. A flap was then removed posteriorly to show the tendo Achillis, the flexor tendons, and the ligaments at the back of the ankle. The points noted were that ordinary dorsiflexion produces eversion of the heel, and that forced dorsiflexion accentuates this movement. Continuation of the force caused the body of the talus to appear between the stretched tendons of the flexor longus hallucis on the lateral side and the tendons of flexor longus digitorum and tibialis posterior on the medial side. The tendo Achillis assumed a position definitely lateral to the midline of the talus. Full manual strength was unavailing to dislocate the body of the talus; the deep deltoid fibres, though very tense, did not give way. The interosseous ligament was then cut through, and the forcible movements repeated; no substantial change in the results was obtained. Next an attempt was made to produce a thrust by fixing the heel and bringing pressure to bear through the lower surface of the tibia on the anterior lateral portion of the cut surface of the body of the talus, *i.e.*, pressure downwards, backwards and medially. The result of this was to push the body of the talus more forcibly between the flexor longus hallucis and flexor longus digitorum (see drawing). The experiment was not carried to the point of actual dislocation.

The mechanism of fracture without dislocation

is fairly easily understood. At the time of the accident the foot is forced into dorsiflexion beyond the normal limits. The line of strain passes through the metatarsal shafts, especially the lateral four, through the cuneiforms and the navicular to the head of the talus. Any part of this line may give way. The fracture may in-



Drawing of foot: (1) Tendon of flexor digitorum longus; (2) talus; (3) tendon of flexor hallucis longus; (4) talo-fibular ligament.

volve the shafts of the metatarsals, the cuneiforms may be crushed, but generally the brunt of the shock is borne by the navicular and the head of the talus where these two bones articulate. Should the force continue without any of these parts having given way, the anterior border of the lower articular surface of the tibia acts as the apex of a wedge, cleaving the neck of the bone from above downwards, and, owing to the impact of tibia on lateral part of the neck of the talus, from the lateral to the medial side; the neck being cleft, the body of the talus is squeezed backwards. But backward displace-

ment of the body is very rare unless accompanied by rotation. What determines the rotation? Mercer considers that this is a matter of chance, depending on the angle at which the part hits the tendo Achillis, the loose fragment passing to the medial or to the lateral side according to whether the medial or lateral side of the tendon is struck. It is probably incorrect to visualize the posterior fragment as completely detached and being projected against the taut tendo Achillis as against a bowstring.

When posterior dislocation of the body of the bone occurs the mechanism is probably as follows. Strong dorsiflexion of the foot occurs, leading to fracture through the neck of the talus; very strong eversion of the heel takes place, accompanied by a thrust downwards, medially and backwards, the heel being fixed; this brings pressure on the anterior and lateral aspect of the body of the bone. The direct backward displacement of the part is resisted mainly by the tendon of the flexor longus hallucis, which is strongly curved and exerts pressure, not merely forwards but by means of the lateral part of the posterior process in a lateral direction. The torque thus produced thrusts the body of the bone into and sometimes actually through the "button-hole" formed by the flexor tendons (see drawing). This involves tearing of the fibres of the interosseous ligament, of the posterior ligament of the ankle-joint, and of the deep fibres of the deltoid ligament. The posterior talo-fibular ligament becomes tense, but does not give way, defended as it is by the strong tendon of the flexor longus hallucis. If the body of the bone passes through the button-hole, it is attached only by the posterior talo-fibular ligament. Tethered to this, it swings round into the position described, where the broken surface looks directly downwards. Incidentally, replacement of the posterior fragment through the button-hole must be more difficult, and the loss of blood supply associated with tearing of ligaments must be much more serious than when the displacement is less pronounced.

PROGNOSIS

This is generally referred to as bad. The gloomy outlook may be correlated with the frequency with which the fracture is overlooked until a late date. Thus Cabot and Binney, reporting on 8 cases, described the results as good in 2 and bad in 6. The period of disability is

reckoned in many months, and in the opinion of some writers recovery is never complete.

TREATMENT

Each case must be treated as an individual problem. Where there is crushing of the anterior part of the bone, manual remodelling, followed by rest in splints, plaster or otherwise, and the use of stabilizing apparatus such as an iron and T-Strap may be all that is necessary. When the body of the bone is crushed, alignment of foot and leg is the crux of the problem and may necessitate a subtaloid arthrodesis, or some other form of plastic bone-work about the posterior tarsus.

When the posterior fragment is displaced backwards, three methods are available for consideration: (1) reposition of the fragments; (2) removal of the displaced fragment and partial talectomy; (3) complete talectomy.

Reposition of the fragments.—Mercer suggests that by flexion of the knee-joint sufficient relaxation of the tendo Achillis can be obtained to permit of manipulative replacement, and if this result is not possible the displaced fragment should be removed. Dean Lewis states "If recognized at the time of injury, it is impossible to reduce the same except in one way only, and that is to do a tenotomy of the tendo Achillis." In two of the following cases the tendo Achillis was not divided but the peroneal tendons were. The displaced fragment was put in correct alignment without much difficulty, and the severed tendons were re-united with silk, the operative result being satisfactory.

Partial talectomy.—This has been found a satisfactory measure by some observers. Speed suggests removal of the displaced fragment "if it cannot be perfectly replaced by manipulation or open operation. The fixed part may safely be left and good movement with no shortening of the ankle results." On the other hand, Mowell feels that it is better to take out the entire talus, so that the articular surface of the tibia will come further forward on the foot. Otherwise the tibia will settle down on the retro-articular part of the calcaneus. The criticism is valid. In one of the following cases, partial talectomy had been done and was followed later by complete talectomy.

Complete talectomy.—It was suggested that callus formation might interfere with movement at the ankle-joint, should reposition be at-

tempted, or that necrosis of the anterior fragment might occur if it were left behind. Speed states that open operations for reduction of the fragments by simple reposition do not promise well. Excision of the bone is reached ultimately in most cases. He makes the point that in recent cases the danger of infection from devitalized soft parts is very great. Two of our cases were treated by open reposition, one immediately, the other four days after injury; in neither case did infection occur. The danger of infection should not be exaggerated.

Three case histories are given in which there was injury to the talus without displacement, and 3 in which displacement of the posterior fragment was the outstanding feature.

CASE 1

S.O., a male, aged 30, was seen at the outdoor clinic complaining of pain in the left foot. His history was that five years before being seen he had fallen off a horse, injuring the left foot. For two months he had been unable to walk on the foot. Since then he had worked as a labourer, although the foot had always been painful.

Examination showed the foot to be quite flat (Fig. 1), the navicular tuberosity being in contact with the floor. X-ray (Fig. 2) showed that there had been a crushing of the head of the talus in its upper and medial portion.

The surgical procedure in this case would be to bring about fixation of the talus and navicular, raising at the same time the longitudinal arch of the foot. The patient had been in Canada for only a year and was extremely desirous of returning to his fatherland, so, on economic grounds, it was decided to recommend his deportation, and this was accordingly done.

CASE 2

M.L., a male, aged 46, was seen for the first time at the outdoor clinic on May 11, 1931, complaining of pain in the left foot. On October 23, 1930, he had fallen from the top of a box car to the ground, a distance of about twelve feet. He fractured the head of the talus, the navicular, and the bases of the four outer metatarsals (Fig. 3). The foot was in plaster of Paris for five weeks; he walked for the first time two months after the injury. He now complained of pain in front of the ankle and in the instep. He was advised to submit the foot to reconstruction, but did not return to the Clinic.

This case (Fig. 4, May 11) illustrates what happens when the stress of the applied force expends itself upon the forepart of the foot. Dislocation of the body of the bone would not be expected in this case; the strain was taken up almost in its entirety before reaching the talus.

CASE 3

J.H., a male, aged 27, was sent by the Workmen's Compensation Board. On March 2, 1932, he fell down a hole, injuring his heels and ankles. The left heel

recovered almost completely; the right continued to be much displaced. Pain was felt on the outer side of the ankle and about the subastragaloid joint. The patient was able to walk only with the help of a cane. The right heel was considerably everted, and the x-ray showed a crushing fracture of the calcaneus and of the body of the astragalus.

On August 18, 1932, the right ankle region was opened up. It was found that there had been a good deal of crushing of the distal surface of the body of the astragalus, as well as of the calcaneus. When the foot was replaced in good alignment with the leg, it was not possible to avoid a large gap between these bones. Accordingly a section was removed from the shaft of the fibula, split, and used as a series of grafts. The limb was put up in plaster (Fig. 5). On September 22nd, the patient was permitted to put a little weight on the foot, and on October 6th, the plaster was removed. A boot was procured with an outside iron and a T-strap. The patient returned to his home five hundred miles away and was not seen until April 20, 1933. On this date union was apparently solid, although the alignment of the foot and leg was not as good as immediately after the operation. He stated, however, that there was less discomfort in the right foot than in the left (Fig. 6).

In this case it might have been better to have restrained the patient from weight-bearing for a longer time. This might have given a better anatomical result. Functionally, there is little to be desired. The loss of a portion of the fibula does not seem to cause any measurable degree of disability.

CASE 4

A.D., a male, aged 30, was seen on November 5, 1926. In April, 1926, he had fallen into an old well, sustaining an injury to the right astragalus. The body of the bone had been displaced backwards. The surgeon who attended to him removed the posterior portion of the bone the same evening. He had plaster applied to the foot and leg for about ten weeks after the accident. When seen he was unable to walk without the help of a cane, and was a heel-walker. No movement was possible at the ankle joint. On November 9, 1926, the anterior portion of the talus was removed. A bed was made for the external malleolus on the lateral side of the foot. On January 25, 1927, all plaster was removed, and it was possible for him to put on a shoe. A raise of half an inch was put on the heel. Seen again on September 12, 1927, he reported a good deal of pain under the head of the fifth metatarsal. It was noted that the front part of the foot was somewhat inverted. No further report has been received since that date, but an enquiry from his doctor produced the x-ray shown (Fig. 7, October 1, 1933).

In this case a trial was given to the procedure of partial talectomy. Three months of rest were followed by three months of activity. The result was unsatisfactory. A farmer may manage to get along as a heel-walker, but from every point of view he is better to be independent of a cane.

CASE 5

J.P.G., a male, aged 40, crashed in an aeroplane on August 23, 1929. The injuries were many and severe. His face was badly cut; the right femur was badly comminuted about the middle of the shaft, and alongside this was a flesh wound. The lower end of the femur was fractured into the knee joint. The right astragalus was fractured, and the body of the bone

driven backwards. The left ankle was fractured, both malleoli being broken (Fig. 8a).

The patient was seen about an hour after the accident. It was judged advisable to deal with the fractured astragalus by open operation. The ankle-joint was opened by an external incision, the peroneal tendons cut across and the foot strongly everted. It was then comparatively easy to replace the fractured pieces of bone in normal relationship (Fig. 8b). The peroneal tendons were then sutured, the wound closed, and the foot and leg put up in plaster of Paris. The convalescence was rather stormy, but the patient appreciated the necessity of securing movement and gave ideal cooperation. The result is excellent. The patient cannot assume as complete a squatting position on the injured as on the uninjured side, but he walks without a limp, is free from pain, and carries on the full work of a very busy medical practitioner.

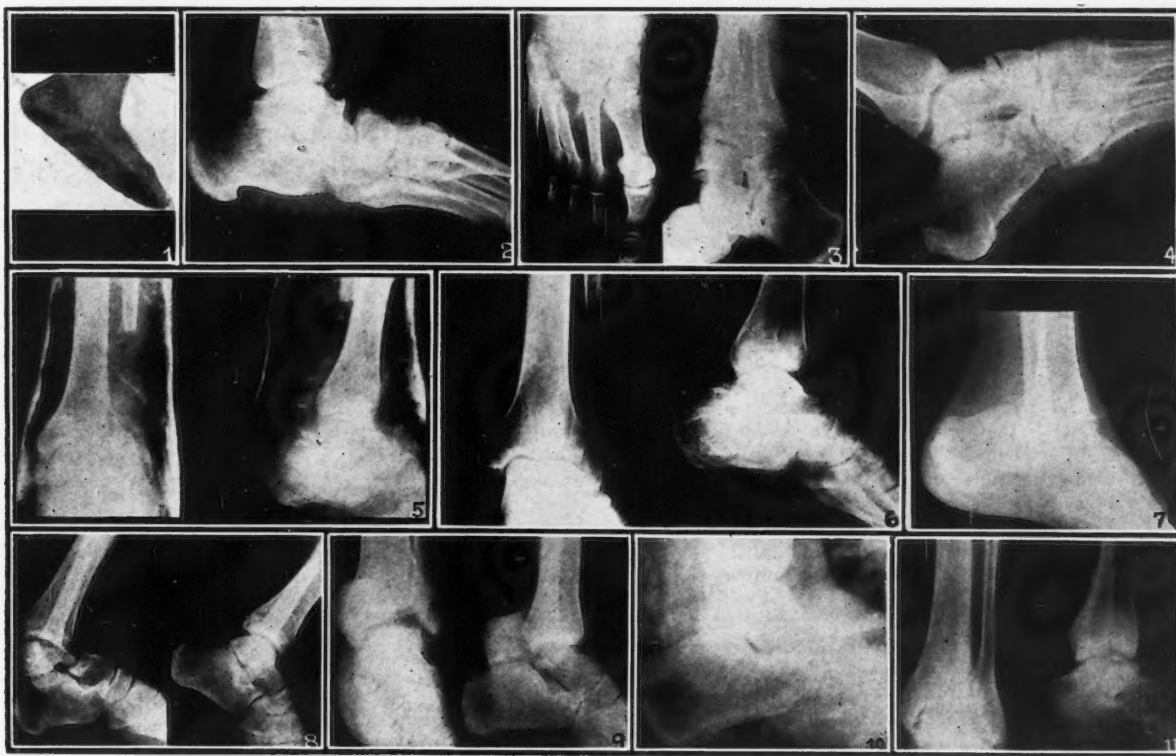
Up to the present the result in this case is entirely satisfactory; whether osteo-arthritis changes will appear later on remains to be seen. The gratifying result is attributed to three main factors: early interference before the soft parts had been subjected to prolonged congestion; the perfect cooperation of the patient; a less severe displacement. X-ray (Fig. 8a) shows: (1) the body of the talus has engaged in the button-hole but has not passed through it; (2) the tendo Achillis is in full contact with the body of the talus.

CASE 6

D.McG., a male, aged 32. On August 4, 1930, the patient was travelling on a railroad speeder. On rounding a corner, he observed a freight train approaching; he threw himself from the speeder, sustaining a fracture of the right astragalus. This occurred some six hundred miles north of Winnipeg, and it was not until August

7th that he was under competent medical care. The ankle region was enormously swollen and x-ray showed a fracture of the talus through the neck, with backward displacement of the posterior fragment (Fig. 9, after reposition). On August 8th, the area was opened by external incision. The soft parts were very congested, and reposition of the fragments was not entirely easy (Fig. 10). On August 20th, the stitches were removed, the plaster discarded and movement commenced. The wound, though clean, was not solidly healed. On October 1, 1930, it is noted that the patient was walking with a fair amount of freedom. On December 2nd the swelling about the ankle was observed to be greater than previously and there was considerable heat in the part. He had returned to office duty about the middle of October, but had had to desist from walking about. On February 21, 1931, an x-ray showed the fragments in good position, but there was considerable rarefaction of the bones. Relative rest from weight-bearing was prescribed, and on June 10, 1931, it was noted that the foot could be brought easily to a right angle and that the swelling was less. Movement was commencing in the subastragaloid joint. The swelling of the part persisted in an unsatisfactory way. Throughout 1932 x-rays were taken at intervals, and it soon became evident that a good deal of necrosis was taking place in the astragalus and in the adjoining part of the tibia. Clinically, rough grating was present in the ankle-joint on active or passive movement, but this was not accompanied by pain, except after prolonged walking. On December 15, 1932 (Fig. 11), the note was made: "The x-ray which was taken today shows still further disintegration of the astragalus and of the adjoining tibial surface. Will have to consider further interference. Possibilities: astragalectomy, not promising in this case; arthrodesis both sides of the astragalus; doubt here because of quality of bone; Syme's amputation, soft parts not at all satisfactory; amputation through the leg probably the best solution."

On January 2, 1933, the leg was amputated about 7½ inches below the knee. Some three months later he was fitted with an artificial limb, and the functional result is satisfactory, though amputation for this condition can only be regarded as a confession of failure.



FIGS. 1 TO 11.

It is interesting to enquire why this case proceeded to this termination when another almost precisely similar obtained successful healing. This patient was younger, he was accustomed to an outdoor life, the Wassermann test was negative, and yet necrosis of the bone involved took place quietly and aseptically. Examination of the amputated part was carried out in the Department of Anatomy, and it was found that the posterior tibial artery was extremely small, practically all the blood supply to the talus having been received from the anterior tibial. Apart from this congenital variation, the blood vessels all showed much thickened walls.

Would the result have been different if a "pan-astragaloid arthrodesis" had been performed immediately, *i.e.*, if the articular surfaces of talus, calcaneus and lower end of tibia had been removed? The body of the talus would then have been essentially a bone graft with blood supply from two additional sources, and might thus have had a better chance of survival. On the other hand, the later x-rays showed that these bones themselves manifested the effects of poor blood supply; the result therefore might have been the same. The most important factor in the ultimate outcome was undoubtedly the fact that in this case the body of the bone had passed through the button-hole, tearing all ligamentous connections except the posterior talo-fibular ligament, and consequently interrupting all blood supply except what this ligament carried. The supply through the deep deltoid ligament was certainly cut off. Delay in the receipt of attention may have led to vascular changes, manifested by the prolonged congestion.

It is permissible to conclude that in cases of posterior dislocation of the body of the talus,

the x-ray will give information as to the amount of ligamentous damage, and therefore of interruption of blood supply. Should the body of the bone appear at the button-hole, but not be forced through it, the chances of complete recovery by operative reposition are good. On the other hand, should the body of the bone be forced through the button-hole, this means that the blood supply coming by way of the deep fibres of the deltoid ligament is destroyed, and there is a likelihood of aseptic necrosis of the part, the blood supply coming via the posterior talo-fibular ligament being insufficient to maintain the nutrition of this mass of bone. In such cases, the choice would lie between complete talectomy, and "pan-astragaloid arthrodesis", *i.e.*, the body might be replaced, but only as a graft producing a solid column from the knee to the heel.

SUMMARY

Fracture of the talus is rare, except as the result of aviation accidents. It may be produced by strong force applied to the forepart of the foot leading to excessive dorsiflexion at the ankle-joint. When this force is pronounced it produces in addition strong eversion of the heel, and if combined with a thrust downwards, backwards, and medially the body of the bone undergoes a torsion strain. As a result of this thrust, the body of the bone may be pushed into or even through the flexor "button-hole".

Partial talectomy is unsatisfactory.

Complete talectomy may be satisfactory.

Reposition may give a completely satisfactory result if the blood supply of the fragment is sufficient; otherwise, complete talectomy or "pan-astragaloid arthrodesis" should be the measure of choice.

EFFECTS OF TOBACCO ON THE PERIPHERAL VASCULAR SYSTEM.—I. S. Wright and D. Moffat observed that the smoking of tobacco in the form of "standard" cigarettes produces in the great majority of normal subjects certain definite pharmacological effects: (1) A marked drop in surface temperature occurs at the tips of the fingers and toes. This varies in different persons with the same tobacco and in the same person at different times. The average drop in their series was 5.3 degrees F.; the maximal drop was 15.5 degrees F. Surface temperature taken at the forehead and waist did not show a similar change. (2) Slowing and stoppage of the blood flow in the capillaries of the nail fold were frequently observed during these tests. The length of time a subject had been a smoker and the number of cigarettes habitually smoked daily had no determinable effect on the degree of the temperature drop. Certain subjects showed marked

toxic effects from smoking one cigarette under controlled conditions. In each instance, these were experienced smokers who ordinarily note slight or no symptoms from smoking. No direct relationship between the degree of drop in peripheral surface temperature and the skin tests for tobacco and nicotine could be established. The lack of symptoms noticed by experienced smokers, under usual conditions of smoking, is probably, at least in many instances, not due to the development of an immunity to the toxins of tobacco smoke but rather to a conscious or subconscious control of the rate and depth of inhalation, which keeps the toxic effects at a sub-manifest level. Although not definitely proved, the evidence seems to indicate that nicotine is at least one of the toxic factors and that carbon monoxide and the products of the cigarette papers may be eliminated as offending mediums.—*J. Am. M. Ass.*, 1934, 103: 318.

RAPID CARDIAC FAILURE AS A SYMPTOM OF ACUTE LEUKÆMIA*

BY CHARLES A. MARKSON,

Toronto

THE diagnosis of the case to be presented is perhaps doubtful. Nevertheless, its history does bring home the point that weakness of unexplainable origin may be due to progressive myocardial failure.

Of the many striking forms in which acute leukæmia may appear none are better disguised than that in which there are signs of heart failure and no early clear-cut blood picture. A case with such masking of its true form has recently been under my observation. Lacking the florid manifestations so often a feature of the acute leukæmic syndrome, one was hard put to explain the symptoms of the earlier days of the patient's illness. Lulled into a feeling of false security by the findings in the preliminary blood examination, I failed to recognize till the last day of the patient's illness the existence of the condition which underlay the acutely developing cardiac weakness. The fortunate circumstances of having made other blood preparations in the final hours and of finding the specimens of earlier date allow one however to suggest a satisfactory explanation of a difficult problem. It emphasizes moreover the value of a simple form of examination, which should be done as a matter of routine, namely, the making of a blood smear.

CASE REPORT

The case in question was that of a man of 34, who up to about two and one-half weeks before death had always enjoyed good health. He consulted me with regard to a pain in the right side of his chest and right shoulder. This seemed to be explained by the finding of a pleural rub low in the right back, above the liver. A pain of similar nature, complained of a few days later on the left side, seemed to be explained in the same way, but in the matter of a few days the symptoms in relation to the chest disappeared, leaving some signs of fluid at the left base. A slight irregular fever and some fugitive pains in the shoulder joints suggested that perhaps a rheumatic infection might be in the background. The man remained well nourished and cheerful, but looked pale and made the persistent complaint of extreme weakness and dyspnoea on the slightest effort. The pulse rate was unusually high in relation to the slight degree of fever. Seen a few days later, the complaint of weakness was reiterated, and as there was nothing to explain this extreme weakness, with its accompanying rapid heart action, a complete check-over of the blood was made. The report was that there was

no severe anæmia, but that the white blood count totaled 20,000, with a distinct increase in the percentage of the mononuclear cells. Further investigation along the lines suggested by this blood count revealed no glandular enlargement, no splenic tumour, and no tenderness over the long bones or sternum. On account of the distinct pallor the question of anæmia and leukæmia came up. There were no hæmorrhages into the skin or elsewhere. Blood culture and the Wassermann test were negative. As noted, the pulse rate had risen and a careful examination of the heart showed only a slight increase in size, with no suggestion of pericarditis or pericardial effusion. A distinct gallop rhythm had developed, however, and the doubling of the impulse was clearly visible on inspection. There was nothing in the eye-grounds; the throat showed no sign of infection. The urine showed a trace of albumin and a few red blood cells. Of interest in this connection is the statement that two weeks previously the urine had looked as if blood-stained. This bloody appearance seemed to have followed the administration of some drug.

By the next day the patient appeared desperately ill. He did not seem to be any more anæmic; the breathlessness was pronounced, without there being fluid demonstrable in chest or pericardium; the liver was now distinctly swollen; the heart rate rapid and the gallop rhythm outspoken; slight œdema of the ankles had appeared. A myocardial failure of undetermined origin seemed best to explain the condition now present.

The blood findings up to this time were scarcely sufficient to allow one to say that an acute leukæmia, rather than an infection, was the condition underlying the rapid decline. One might well be excused for considering that the lymphocytosis of 50 per cent was merely an unusual response to one of the many types of infection which tend to produce an increase in the small mononuclear cells. The general picture presented by the blood smear at this time was not enough, certainly, to arouse the suspicion of leukæmia in the mind of a well trained technician. It is true, as one goes again carefully over the specimens, that certain elements look threatening in view of later findings, but cases of well marked lymphocytosis are no rarity in a general laboratory.

Twenty-four hours later the end was in sight. The dyspnoea had become intense, the heart was racing in a well marked gallop rhythm, and the liver was tender and swollen; the urine contained no sugar. No fluid was found in the chest on puncture; none could be demonstrated in the pericardial sac, even in the erect posture. A careful screening, twenty-four hours previously, had shown the chest to be clear, nor had any particular enlargement of the heart been demonstrated. A few hæmorrhages into the skin appeared along the course of scratch marks. A most careful examination failed to find splenic or glandular enlargement. The œdema had spread to the knees and buttocks. A blood smear made at this time seems finally to explain the man's curious illness, for it showed now in his last hours what must be looked upon either as an intense myelosis appearing as a terminal event, or as a picture of a leukæmia developing acutely within a matter of a few days. Death occurred as the man sprang up in bed in the extremes of dyspnoea.

A comparison of the blood specimens taken within a few days of each other shows interesting differences. The first specimen, taken two

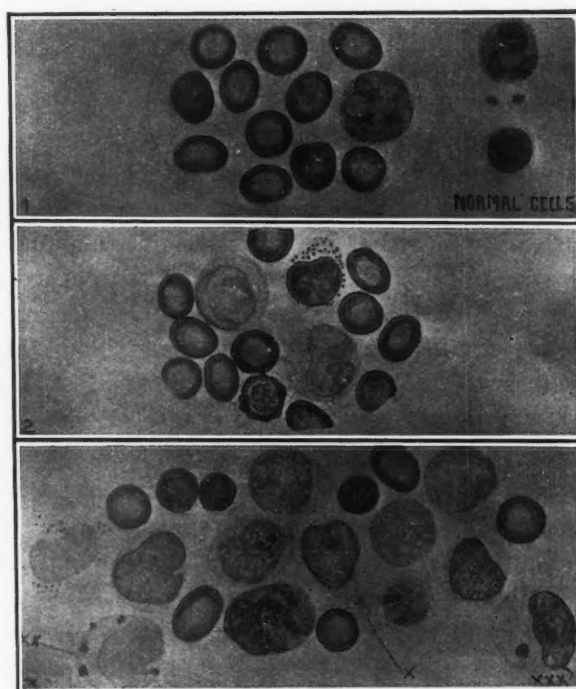
* Presented at the Section of Medicine, Academy of Medicine, Toronto, December, 1933.

weeks before death, showed merely a suggestion of anaemia with a slight increase in the white cells and an increase in the percentage of the mononuclear elements, not in itself very suggestive. In the second group of smears there was more evident leucocytosis and, as mentioned, a perceptible increase in the percentage of lymphocytes or mononuclear cells. To the laboratory assistant, however, as already mentioned, the major portion of this second group of slides did not seem to present the picture of a leukæmia; it is only on re-examining these slides that one finds in corners certain grave suggestions in the presence of an occasional megaloblast, a rare myelocyte, and what one may prefer to call monocytes, a cell which in the older descriptions of the blood would pass as a large mononuclear or large lymphocyte. In many parts of the slides the increase of white cells is by no means apparent, yet now one feels that the suspicion of a developing leukæmia might well be aroused by the chance findings recorded, in spite of the fact that a preliminary report on these same slides contains no mention of this disease. The final lot of specimens made on the day of death indicate that either an intense myelosis due to a marrow response to some unknown evil was in existence, or that an acute leukæmia was explaining the rather mysterious heart failure. The absence of glandular and splenic enlargement was noteworthy.

The proof of the existence of a leukæmia by autopsy is lacking, but the blood smear would seem to be conclusive, and one's feeling is that the distinctly obscure nature of the illness from which the patient died is best explained on the basis of acute leukæmia. The absence of glandular and splenic enlargement is not unusual in the very acute forms of this disease, and though at times when the bone marrow has been invaded by tumour-growth, as in Hodgkin's disease or lymphosarcoma, such remarkable pictures as the one before us may be presented, yet in this case no sign of such disorders had been in evidence during the patient's illness. Interesting examples of this nature have been frequently reported, and, with invasion of the hæmatopoietic tissues, one may expect bone marrow responses which at times may be most confusing. As stated, the possibility of our case having been merely an extreme myelosis is admitted. The probability remains, however, that he was an interesting example of the many

obscure forms under which an acute leukæmia may present itself. The specimens may be briefly described.

Fig. 1.—from the second group of specimens made three days before death. This shows many cells much larger than the ordinary lymphocyte and with a distinctly pale and mauve-coloured nucleus with the Wright stain. These have the appearance of immature cells, the dark, deeply-stained nucleus of the lymphocyte presenting a much different picture. The larger cell to the right has a convoluted rather



than a lobulated nucleus. It shows beginning granulation. This cell may belong to the so-called monocytic group. (A polymorphonuclear cell is inserted further to the right.) These cells with their convoluted nucleus and slight granulation have probably passed as polymorphonuclear cells.

Fig. 2.—from the same group of specimens. A megaloblast with a well defined young nucleus is shown; a myelocyte with coarse granulations is also to be seen; two cells which according to the old nomenclature would be called large mononuclear or transitionals are depicted. One of these is finely speckled with granulations and conforms closely with the description of the monocyte of some writers. The grouping of the cells in these two plates was only noted after prolonged search. No specimen of very unusual nature had been apparent in the casual examination, and a report

of a lymphocytosis had been made from fields such as shown in plate one.

Fig. 3.—made a few days later, and only shortly before death, gives a definite impression of an acute leukæmia. A few distinct myelocytes are present in each field, but the majority of the cells are large cells with large pale nuclei, oval or lobed and surrounded by a scanty granulation. These cells resemble closely those pictured by Clough in his article on "Monocytic leukæmia" (*Johns Hopkins Hosp. Bull.*, 1932, 51: 148), but one hesitates to call our case one of this type of leukæmia without further investigation. To some observers this particular cell appears as the pre-myelocyte; to others it is a monocyte which has developed from a smaller lymphocyte; to yet others it is a special production of the great reticulo-endothelial system, and has a relationship to the various forms of white cells which is by no means well understood. Of interest in the cytological study is the cell marked "X", which appears to have been caught while in the process of amœboid motion. Many such cells were to be seen. This faculty of amœboid motion seems to belong more to the so-called monocytes and histiocytes. Phagocytosis was observed as

indicated in "XX".* This may explain the great scarcity of platelets in the preparation. The curious inclusion in the cell marked "XXX" may represent an ingested cell nucleus.

In debating the nature of the disease from which our patient died one naturally gives consideration to such conditions as infectious mononucleosis. Evident of local infection however were absent. The scarcity of polymorphonuclear cells was evident, as was the diminution in the number of platelets. The suspicion of agranulocytosis does not however seem justified. A myelosis or a real leukæmia is the picture presented. Without question, many of the terms as applied to the blood cells are confusing to a degree, and the proof of the relationship of the large cells here depicted to marrow cells, to lymphocytes or to stem cells, absorbs the interest of several schools of observers. We were unfortunate in not being able to obtain an autopsy, and hence have no specimens showing bone marrow alterations. Our feeling, however, is that our patient died as the result of an acute leukæmia characterized by the presence in the circulating blood of a rather unusual form of marrow cell.

* Unlike most cases of leukæmia platelets were very scarce throughout all the preparations. The cell "XX" seems to have ingested platelets in considerable number.

THE BLOOD IODINE CONTENT OF NORMAL AND THYROTOXIC INDIVIDUALS. AN IODINE TOLERANCE TEST*

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PART I

FOR some time investigators have been studying the blood iodine content of normal and goitrous individuals. The results of these investigations have indicated that there is no regular or absolute correlation, so far as we know, between the increased blood iodine level of hyperthyroidism and the basal metabolic rate.^{1 to 5} Furthermore, the same negative findings have been reported with respect to the inorganic and organic iodine fractions of the blood.⁶

Various chemical procedures have been de-

vised for the quantitative estimation of iodine in the blood. The greater number of these are either very complicated or require relatively large amounts of blood.^{7 to 10} One of us (H.J.P.) has devised a simple method¹¹ requiring only 10 c.c. of blood and involving an error of less than 10 per cent. This method may be outlined briefly as follows. Ten c.c. of whole blood are collected in a nickel crucible and combusted with potassium carbonate at 500° F. in a muffle furnace for five hours. The ash is extracted with alcohol, filtered, and the filtrate evaporated to dryness. The residue from the filtrate is taken up with water, made slightly acid, and the iodide oxidized to iodate. The addition of

* Read before the Section of Medicine, Toronto Academy of Medicine, March 13, 1934.

potassium iodide frees the iodine, which is titrated to colourless with sodium thiosulphate, starch serving as an indicator. Contamination must be carefully avoided at all stages of the procedure.

Employing this simplified technique, the blood iodine of normal individuals and patients with suspected hyperthyroidism has been studied. In 40 normal individuals, the iodine content was found to vary between 0.24 γ * and 1.85 γ per 10 gm. of whole blood (Chart 1). It would ap-

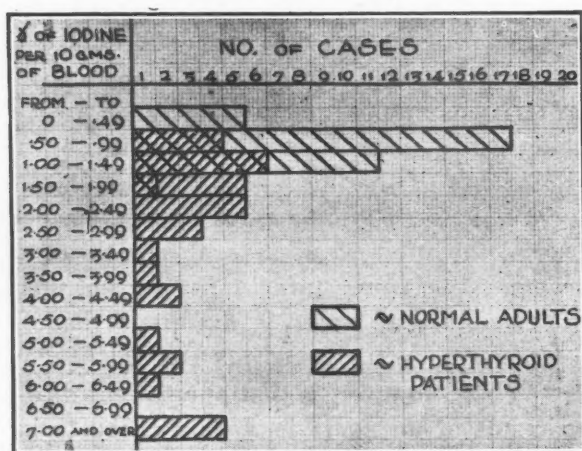


CHART 1.—Illustrating the overlap of the blood iodine ranges for normal and hyperthyroid individuals.

pear from our more recent work that a lesser degree of fluctuation may exist under basal or resting conditions. This was noted in a small group of normals, the range lying between 0.22 γ and 0.64 γ of iodine per 10 gm. of blood.

The blood from 39 patients at the Toronto General Hospital with suspected hyperthyroidism was analyzed for iodine. The range for the group was between 0.72 γ and 14.1 γ of iodine per 10 gm. of whole blood. Histological examination of the thyroid, following operation, revealed 4 cases with no hyperplasia, 3 with malignant change, while the remaining 32 showed varying degrees of hyperplasia. In the group with clinical and histological evidence of hyperthyroidism the blood iodine was increased, the variation being between 1.0 γ and 5.6 γ per 10 gm. of blood (Chart 1).

These results have been obtained during the period of a year, hence some of the variability may be attributed to seasonal influence. It has been reported¹² that during the winter months the blood iodine concentration is reduced, and this fact has been corroborated by us in a few normal cases. As pointed out above, a more

limited degree of variation might be established by securing specimens of blood from the patients, under basal metabolic conditions. The importance of this condition was not recognized until the greater number of these cases had been studied.

PART II

AN IODINE TOLERANCE TEST

In the course of our work we have observed that following the oral administration of Lugol's solution the blood iodine level was considerably increased, varying with the time the blood was taken. This observation led us to investigate in normal individuals the relation of the iodine concentration of the blood with respect to time, following the ingestion of a known amount of iodine. A test was outlined as follows. After obtaining a 10 c.c. sample of blood, 10 minims of Lugol's solution in milk were given by mouth in the morning, breakfast being limited to one cup of coffee and a piece of toast. Five blood samples were withdrawn at $\frac{1}{2}$, 1, $1\frac{1}{2}$, $2\frac{1}{2}$ and 7-hour periods, and the total iodine estimated. The amount of blood taken was reduced to 3 c.c., since the iodine concentration was increased from 5 to 15 times normal. During the day normal meals were taken, with the exception that no foods high in iodine content (*i.e.*, sea-fish) were allowed. Total iodine estimations were made on the urine collected during the 24-hour period. The results obtained in 10 normal individuals are shown in Table I, and three typical normal curves are demonstrated in Charts 2, 4 and 6.

Since an abnormal iodine metabolism is con-

TABLE I.
NORMAL

Case	Sex and Age	B M R	Iodine Tolerance Test Blood Values						Urinary Excretion of Iodine in 24 hrs.
			0 hr.	$\frac{1}{2}$ hr.	1 hr.	$1\frac{1}{2}$ hr.	$2\frac{1}{2}$ hr.	7 hr.	
B.B.	M. 26	- 7	0.6	11.2	...	17.8	15.2	5.1	11.72
H.P.	M. 28	- 10	0.4	15.0	12.0	15.5	13.2	8.0	...
M.M.	M. 27	- 12	0.8	5.4	13.6	16.2	10.8	6.4	12.94
E.O.	M. 29	- 5	1.0	12.8	15.0	21.8	9.3	11.5	13.27
R.A.	M. 29	+ 2	0.6	11.1	...	8.8	7.1	4.3	17.74
J.F.	M. 34	- 13	0.3	12.8	11.7	9.0	7.4	4.8	25.7
S.S.	M. 68	- 17	...	10.3	...	12.6	9.8	6.6	18.44
A.S.	F. 28	- 6	0.6	12.9	...	11.5	10.1	9.2	16.76
B.	F. 45	-	...	17.3	13.2	4.4	6.0	3.2	12.6
H.W.	M. 15	-	...	12.0	12.2	11.9	5.3	13.2	10.29
(in γ of iodine per 10 gm. blood)									(mgms.)

* γ = 0.001 mg.

sidered to exist in individuals with hyperthyroidism, it was thought possible that these patients might indicate in their blood iodine a response different from the normal following the ingestion of Lugol's solution. Accordingly, using the same procedure as that used in the normal group, patients with suspected hyperthyroidism were studied. Table II shows the results obtained in a group of 10 hyperthyroid patients. Three type cases are shown in graph form in Charts 3, 5 and 7.

TABLE II.
HYPERTHYROID

Case	Sex and Age	B M R	Iodine Tolerance Test Blood Values						Urinary Excretion of Iodine in 24 hrs.	
			0 hr.	½ hr.	1 hr.	1½ hr.	2½ hr.	7 hr.		
F.W.	M. 35	+36	2.2	8.5	3.8	4.6	4.7	1.4	10.69	
W.S.	M. 45	+37	0.6	8.5	9.2	8.9	7.2	
J.A.	M. 42	+60	1.5	5.5	4.4	3.6	1.5	7.36	
M.Mc.	M. 36	- 4	0.7	4.6	7.9	4.8	9.0	7.74	
C.W.	F. 29	+47	1.2	2.6	7.4	8.8	6.0	8.51	
K.P.	F. 40	+48	0.3	5.9	5.7	4.6	4.4	
C.	F. 38	+50	0.5	5.2	4.8	3.0	5.5	4.9	
I.M.	F. 48	+15	4.1	5.5	5.5	3.1	1.7	15.5	
A.S.	M.	+34	0.3	8.0	4.2	4.4	3.5	1.4	4.2	
A.C.	F. 40	+50	0.2	9.6	7.3	4.6	4.5	1.8	13.3	
(in γ of iodine per 10 grm. blood)										(mgms.)

Analysis of the graphs shows that the blood iodine concentration did not increase to as high a level in patients with a clinical and histological picture of hyperthyroidism as in normal individuals. This is shown more clearly by the relationship of the blood iodine curves to a line arbitrarily drawn at the 10 γ level. It can be readily seen that the hyperthyroid curves for the most part fall below, while the normals all rise above this hypothetical line. Such a finding might be accounted for on the grounds that a hyperplastic thyroid gland may have a greater affinity for iodine than a resting gland, and thus leave less iodine in the blood stream. However, it may be that there is an increased metabolism of iodine in the hyperthyroid individual, although the amount of iodine excreted in the urine in these cases, in comparison with the normal, would not confirm such a hypothesis.

In spite of the fact that an interpretation of the above phenomenon has not been arrived at, the results indicate that estimating the blood iodine concentration at definite intervals, following the ingestion of a single dose of Lugol's solution, may be a valuable guide in the diagnosis of hyperthyroidism.

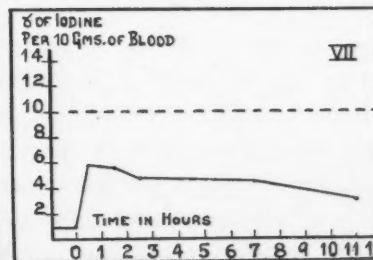
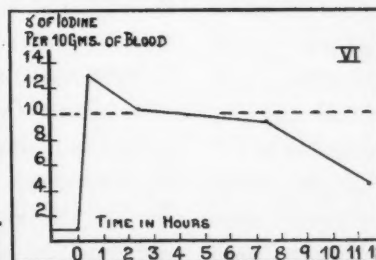
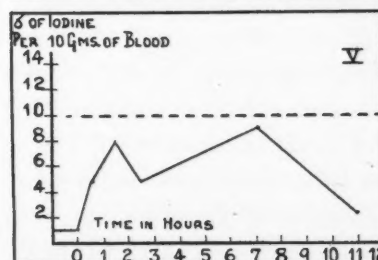
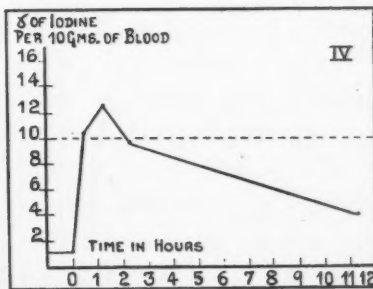
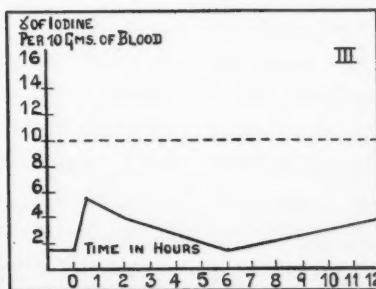
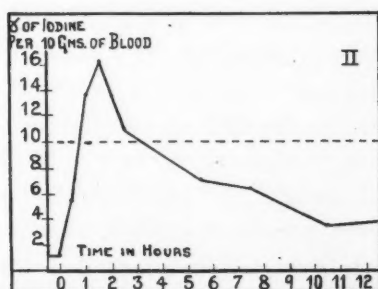


CHART 2.—M.M., 27 yrs., male; normal adult. Urinary iodine (24 hrs.) 12.94 mg., or 26 per cent.

CHART 3.—J.A., 42 yrs., male. Clinical diagnosis, diffuse goitre and hyperthyroidism. Pathological diagnosis confirms. Basal metabolic rate, + 53 + 69. Urinary iodine (24 hrs.) 7.36 mg., or 15 per cent.

CHART 4.—S.S., 68 yrs., male; normal adult. Urinary iodine (24 hrs.) 18.44 mg., or 37 per cent.

CHART 5.—M.Mc., 36 yrs., male. Clinical diagnosis, nodular goitre without hyperthyroidism. Pathological diagnosis, multiple hyperplastic adenomata. Basal metabolic rate, -3. -5. Urinary iodine (24 hrs.) 7.74 mg., or 15 per cent.

CHART 6.—A.S., 28 yrs., female; normal adult. Urinary iodine (24 hrs.) 16.76 mg., or 34 per cent.

CHART 7.—K.P., 40 yrs., female. Clinical diagnosis, nodular goitre with hyperthyroidism. Pathological diagnosis, diffuse hyperplastic goitre (marked). Basal metabolic rate, + 54 + 42. Urinary iodine (24 hrs.), lost.

SUMMARY

1. The iodine content of whole blood has been determined for normal and hyperthyroid individuals of this region.

2. It has been found that the blood iodine of normal persons varied during rest and activity.

3. An iodine tolerance test has been devised which would appear to be of value in establishing a clinical diagnosis of hyperthyroidism.

4. This test can be used clinically, since it requires relatively small amounts of blood.

We wish to thank the Surgical and Medical Services of the Toronto General Hospital for facilities afforded us and for their cooperation in the carrying out of this research.

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A STUDY OF THE RELATIVE ANTIRACHITIC VALUE OF COD LIVER OIL, VIOSTEROL AND IRRADIATED MILK*

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FOR more than one hundred years cod liver oil has been used for the prevention of rickets. The amount of this oil usually administered as an antirachitic is three teaspoonfuls daily.¹ Some six years ago viosterol (irradiated ergosterol) was introduced as a source of vitamin D.² As a result of clinical observations the now accepted dosage of the standard 250D viosterol for the prevention of rickets in the average infant is 10 drops daily.³ By exposure to ultra-violet rays vitamin D can also be developed in milk. Hess and Lewis⁴ in 1933 reported "that an irradiated milk which contains approximately 56 units to the quart (32 ounces) suffices to protect infants against rickets when from 20 to 24 ounces daily is fed".

In order to obtain further information on the relative efficacy of these three antirachitic substances, we have engaged during the past winter in an extensive clinical and x-ray investigation involving over 500 infants. The vitamin D potency of the cod liver oil, viosterol, and irradiated milk was biologically assayed on

rats. In this biological assay the minimum amount of the substance necessary to produce a narrow and continuous line of new bone formation when fed over a period of 10 days to rachitic rats is determined. The amount of antirachitic substance which will produce this degree of healing is spoken of as containing 1 Steenbock unit of vitamin D. The cod liver oil used was a high grade Newfoundland oil containing 130 units per teaspoonful. One teaspoonful of cod liver oil weighed 3.5 grams. Where 3 teaspoonfuls were given per day this was administered as undiluted oil. Where 1 or 2 teaspoonfuls were given daily, sufficient corn oil, which does not contain vitamin D, was added so that the daily dosage of cod liver oil was given as 3 teaspoonfuls of the mixture. The irradiated ergosterol dissolved in corn oil was assayed and diluted so that 10 drops of the different solutions used contained 100, 200, 400 and 800 units of vitamin D. For comparison, 10 drops of the standard 250D viosterol as obtained in drug stores contains 682 units.

The milk used in the observation was ordinary whole pasteurized milk, in which vitamin D had been developed by exposure of the milk to the ultra-violet rays emitted from a

* Read before the 54th Annual Meeting of the Ontario Medical Association, May, 1934.

From the Department of Pædiatrics, University of Toronto, and the Hospital for Sick Children, Toronto.

carbon-arc lamp. The ultra-violet rays act on the ergosterol normally present in milk to produce vitamin D. No change in the taste of the milk is detectable. Throughout the period of observation this milk was found by biological assay to contain 35 Steenbock vitamin D units per imperial pint (20 ounces) of milk, which is 56 units per U.S. quart.

The infants under observation were well babies under home conditions, a group comparable to the babies seen in private practice. The majority were of British and northern European descent; no negroes and only a few

the presence or absence of rickets. The signs noted were craniotabes, bossing, flattening of the back of the head, the rachitic rosary, enlargement of the wrists, and bowing of the long bones. X-rays were then taken of the wrists. The antirachitic materials were supplied to the mothers, who were carefully instructed concerning the dosage and administration. This physical and x-ray examination was repeated in January or February, and final examinations were made in March or April. A space of five months elapsed in each case between the first and final examinations. The physical examina-

TABLE I.
AGES OF INFANTS IN MONTHS AT TIME OF INITIAL EXAMINATION.

	Under 1 month of age	1 month of age	2 months of age	3 months of age	4 months of age	5 months of age	6 months of age	7 months of age	8 months of age	Total
No vitamin D	No.	No.	No.	No.	No.	No.	No.	No.	No.	
1 teaspoonful of cod liver oil daily	1	13	10	7	10	9	9	5	1	65
2 teaspoonfuls " " " " "	0	1	8	5	4	8	3	10	3	42
3 " " " " " " "	0	2	5	8	10	4	7	8	1	45
100 units of viosterol daily	0	7	5	5	6	9	6	10	2	50
200 " " " " " " "	0	9	10	11	4	3	8	3	2	50
400 " " " " " " "	1	10	8	10	3	5	2	5	0	44
800 " " " " " " "	0	12	13	2	6	9	1	1	2	46
1 pint (20 ounces) of irradiated milk daily	1	5	13	7	8	4	4	3	1	46
Over 1 pint of irradiated milk daily	0	8	16	14	8	8	8	7	2	71
	0	0	5	4	13	16	12	11	9	70

Italian babies were included. Their ages ranged from three weeks to eight months on the initial examination in October or November, 1933. At the first observation the infants were divided by rotation into nine groups. The distribution according to ages in the different groups is given in Table I. The first group received 1 teaspoonful of cod liver oil daily; the second group received 2 teaspoonfuls; and the third 3 teaspoonfuls; the fourth group received 100 units of vitamin D in the form of viosterol daily; the fifth group 200 units; the sixth 400 units, and the seventh 800 units; the eighth group received 20 ounces of vitamin D milk daily. Any further milk required was ordinary pasteurized milk. The ninth group received all their milk as vitamin D milk up to a total of one quart (40 ounces). We were also able to observe a number of infants who received no vitamin D.

After the infants had been placed in their respective groups a physical examination was made with regard to the presence or absence of clinical signs usually considered diagnostic of

tions in every case were made by one of the authors (T.G.H.D.).

Throughout the observation the feedings were controlled through the well baby clinics. The infants were followed in their homes by two exceedingly competent nurses trained in public health work, who carefully checked the administration of the antirachitic materials. In case of lack of cooperation in administration of the antirachitic the infant was dropped from the observation. In all, 529 infants were observed throughout the whole period.

After the final x-ray films were taken they were examined for the presence or absence of rickets. The authors are greatly indebted to Dr. Martha Eliot, Department of Pædiatrics, Yale University, for the interpretation of all the x-ray films. The degree of rickets was classified by Dr. Eliot as 1 - , 1, 2 and 3. In this paper we have called Dr. Eliot's Group 1 - , very slight rickets (a barely perceptible change which frequently might not be noted); Group 1, mild rickets (a slight but obvious rachitic change); and Groups 2 and 3, moderate and marked

rickets (well defined fringing and cupping at the end of bone). The interpretation of the x-rays was made without any knowledge of the antirachitic material administered.

In the past considerable work has been done on the antirachitic efficacy of various substances, in which the effectiveness of the materials has been judged on the basis of the clinical examination. We were unable to find any constant relation between the x-ray presence or absence of rickets and the clinical signs. Moderate enlargement of the wrists may be due to the unusual shape of otherwise normal bones. A moderate rachitic rosary was frequently felt, with or without the presence of rickets as shown by x-ray examination of the forearms. In Table II is

TABLE II.
THE INCIDENCE OF ANY X-RAY EVIDENCE OF
RICKETS IN INFANTS WITH CRANIOTABES

Cases of craniotabes.....	79
Craniotabetic cases with rickets at time of craniotabes.....	21
Craniotabetic cases with rickets at any time during observation.....	37

shown the lack of correlation between the presence of craniotabes and x-ray evidence of rickets. The craniotabes noted was not merely softening along sutures but a well marked softening of the occipital or parietal bones, so that pressure dented large areas of these bones in and out, as would the same amount of pressure applied to a large celluloid ball. From these observations it would appear that when dealing with a large group of patients it is only by x-ray examination that the presence or absence of rickets can be determined.

TABLE III.
CASES WITH RICKETS ON INITIAL EXAMINATION
DURING OCTOBER

Total cases.....	349	
Very slight rickets.....	45	= 12.8%
Mild rickets.....	16	= 4.5%
Moderate and marked rickets.....	0	= 0
Total rickets.....	61	= 17.4%
Cases seen in October—1 in every 6 showed some evidence of rickets.		

Three hundred and forty-nine infants were examined during the month of October. Of these infants 17.4 per cent, or approximately 1 in every 6, showed some evidence of rickets (Table III). From this it can be concluded that exposure to summer sunshine as it is now usually being carried out in Toronto is not

entirely efficacious in preventing the development of rickets as evidenced by x-rays.

It has been recognized that rickets is most apt to develop in the early months when the child is growing rapidly. For this reason the infants who were not receiving vitamin D have been grouped in two series; first, those under 4 months of age in October, and, second, those from 4 to 8 months of age in October, the infants in each group being under observation for the subsequent five months (Table IV). This

TABLE IV.
DEVELOPMENT OF RICKETS IN INFANTS OBSERVED FROM
OCTOBER TO APRIL (5 MONTHS) WITHOUT ANTIRACHITIC
TREATMENT.

	Total cases	Very slight rickets	Mild rickets	Moderate and marked rickets
Under 4 months of age in October.....	31	8	6	4
4 to 8 months of age in October.....	34	6	4	1

Table demonstrates the decreased susceptibility to rickets with advancing age. Part of this decreased susceptibility may be due to the beneficial vitamin D effect of summer sunshine, which no doubt was received over a longer period by infants in the older age group. On account of this decreasing susceptibility with age, we have divided all groups on the different medications

TABLE V.
THE EFFECTIVENESS OF COD LIVER OIL IN THE
PREVENTION OF RICKETS AS EVIDENCED BY X-RAYS
Maximum degree of rickets observed at any time
subsequent to initial examination.

	Total cases	Very slight rickets	Mild rickets	Moderate and marked rickets
<i>Under 4 Months of Age at Initial Examination.</i>				
No vitamin D.....	31	8	6	4
(Daily)				
1 teaspoonful cod liver oil	14	2	2	0
2 teaspoonfuls " " "	15	4	1	1
3 " " " "	17	3	1	1
<i>4 to 8 Months of Age at Initial Examination.</i>				
No vitamin D.....	34	6	4	1
(Daily)				
1 teaspoonful cod liver oil	28	3	1	0
2 teaspoonfuls " " "	30	3	2	0
3 " " " "	33	4	3	1

into those under 4 months of age and those 4 months of age and over at the initial examination.

The effectiveness of the daily administration of 1, 2, and 3 teaspoonfuls of cod liver oil in the prevention of rickets, as evidenced by x-ray, over a period of five winter months, is shown in Table V. This Table shows the remarkable fact that one infant for whom 2 teaspoonfuls of cod liver oil daily had been prescribed, and two infants for whom 3 teaspoonfuls daily had been prescribed, developed moderate or marked rickets. The question immediately arises, did these children actually receive the prescribed doses? Greater care was taken to see that they did receive the prescribed amounts of cod liver oil than would be the case in ordinary medical practice. The material was biologically tested; it was supplied free of cost; the mothers were questioned regarding administration by the physician at least three times during the five months' period. The nurses visited the mothers at least once a month, questioned them regarding the administration of the antirachitic, and verified how much had been used from the bottle. Certainly it can be said that these cases of moderate or marked rickets did develop in spite of the prescription of cod liver oil when the probability of the correct administration was as great as if not greater than it would be in ordinary practice. The difficulty in the routine administration of cod liver oil as compared with viosterol or irradiated vitamin D milk is well demonstrated by Table VI.

TABLE VI.

CASES CANCELLED DURING PERIOD OF OBSERVATION
DUE TO UNSATISFACTORY ADMINISTRATION OF
ANTIRACHITIC MATERIAL

Type of Antirachitic Material	Number at start	Number cancelled	Per cent cancelled
Cod liver oil.....	164	14	8.5
Viosterol.....	283	6	2.1
Irradiated vitamin D milk..	156	2	1.3

The effectiveness of the daily administration of 100, 200, 400 and 800 Steenbock vitamin D units of irradiated ergosterol (1.5 to 12 drops of 250D viosterol) in the prevention of rickets, as evidenced by x-ray, over a period of five winter months, is shown in Table VII.

The effectiveness of the daily administration of 1 pint (20 ounces) of irradiated vitamin D

milk, and the entire amount consumed by the infant, 1 pint to 1 quart (40 ounces), in the prevention of rickets, as evidenced by x-rays, over a period of five winter months, is shown in Tables VIII and IX.

The observation of the results obtained on the different medications are grouped together in Tables X and XI.

DISCUSSION

The few infants showing x-ray evidence of mild rickets at the initial examination are not here considered, as the present report deals only with the preventive effect of the anti-

TABLE VII.

THE EFFECTIVENESS OF VIOSTEROL IN THE PREVENTION
OF RICKETS AS EVIDENCED BY X-RAYS

Maximum degree of rickets observed at any time
subsequent to initial examination.

	Total cases	Very slight rickets	Mild rickets	Moderate and marked rickets
<i>Under 4 Months of Age at Initial Examination.</i>				
No vitamin D	31	8	6	4
100 units of viosterol daily	30	6	1	0
200 " " " " "	29	8	1	0
400 " " " " "	27	5	1	0
800 " " " " "	26	5	2	0
<i>4 to 8 Months of Age at Initial Examination.</i>				
No vitamin D	34	6	4	1
100 units of viosterol daily	20	2	0	0
200 " " " " "	15	3	2	0
400 " " " " "	19	4	0	0
800 " " " " "	20	3	1	0

TABLE VIII.

THE EFFECTIVENESS OF ONE PINT (20 OUNCES) OF
IRRADIATED MILK IN THE PREVENTION OF RICKETS
AS EVIDENCED BY X-RAYS

Maximum degree of rickets observed at any time
subsequent to initial examination.

	Total cases	Very slight rickets	Mild rickets	Moderate and marked rickets
<i>Under 4 Months of Age at Initial Examination.</i>				
No vitamin D	31	8	6	4
1 pint (20 ounces) of irradiated milk daily.	38	13	3	0
<i>4 to 8 Months of Age at Initial Examination.</i>				
No vitamin D	34	6	4	1
1 pint (20 ounces) of irradiated milk daily.	33	3	3	0

TABLE IX.
THE EFFECTIVENESS OF OVER ONE PINT (20 TO 40 OUNCES)
OF IRRADIATED MILK IN THE PREVENTION OF RICKETS AS
EVIDENCED BY X-RAYS

Maximum degree of rickets observed at any time
subsequent to initial examination.

	Total cases	Very slight rickets	Mild rickets	Moderate and marked rickets
<i>Under 4 Months of Age at Initial Examination.</i>				
No vitamin D	31	8	6	4
Over 1 pint (20 to 40 ozs.) of irradiated milk daily..	9	5	1	0
<i>4 to 8 Months of Age at Initial Examination.</i>				
No vitamin D	34	6	4	1
Over 1 pint (20 to 40 ozs.) of irradiated milk daily..	61	6	1	0

rachitic procedures under observation. Infants exhibiting very slight rickets on the initial examination are included because of the very minor nature of the rachitic changes present. Since the purpose of the administration of any antirachitic is to prevent the development of rickets, we have considered that the appearance of rickets at any time during the whole course of the observation subsequent to the initial examination is more important than the presence of rickets at the conclusion of the period. As the object of this study is to observe the relative efficiency of various antirachitics on a cross section of the infant population, both breast-fed and arti-

ficially fed infants have been included in the observation. The infants were placed in the various groups by rotation and in Table XII will be seen their distribution in the various groups studied. Naturally, the higher percentage of the infants in the 4 months of age and over group was artificially fed.

It is well recognized that premature babies are more susceptible to rickets than full-term infants. Out of the 529 cases under observation there were 60 prematures, whose distribution in the different groups is shown in Tables X and XI. Of the 60 premature infants 3 developed moderate or marked rickets, while of the remaining 469 full-term infants 8 developed moderate or marked rickets. The distribution of the premature infants in the different groups makes it improbable that their presence significantly alters the relative results.

Infants gaining in weight more slowly than normally are not as susceptible to rickets as the normally or rapidly growing infant. The rate of growth of infants in the different groups has been tabulated in Table XIII. Very few of the infants were markedly under weight. A survey of the figures indicates that it is improbable that this factor alters the relative results to any extent. The only food consumed by these infants which might contain appreciable amounts of vitamin D is egg yolk. A survey was made of the number of infants in each group who received eggs at any time during the period of observation. In very few

TABLE X.
RICKETS AS EVIDENCED BY X-RAYS IN INFANTS UNDER 4 MONTHS OF AGE AT INITIAL EXAMINATION.

Feeding	Number of infants	Number prema- ture infants	Rickets observed at initial examination.				Maximum rickets ob- served at any time after initial examination.				Rickets observed at final examination.			
			No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets	No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets	No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets
No vitamin D	31	3	29	2	0	0	13	8	6	4	14	7	6	4
1 teaspoonful of cod liver oil	14	2	13	1	0	0	10	2	2	0	11	1	2	0
2 teaspoonfuls " " " "	15	2	14	1	0	0	9	4	1	1	11	2	1	1
3 " " " " " "	17	1	17	0	0	0	12	3	1	1	13	2	1	1
100 units of viosterol.....	30	1	30	0	0	0	23	6	1	0	27	3	0	0
200 " " " " " "	29	1	29	0	0	0	20	8	1	0	26	3	0	0
400 " " " " " "	27	2	25	2	0	0	21	5	1	0	23	4	0	0
800 " " " " " "	26	1	25	1	0	0	19	5	2	0	21	5	0	0
1 pint of vitamin D milk....	38	5	34	4	0	0	22	13	3	0	27	8	3	0
Over 1 pint of vitamin D milk	9	0	9	0	0	0	3	5	1	0	7	2	0	0
Total	236	18	225	11	0	0	152	59	19	6	180	37	13	6

TABLE XI.
RICKETS AS EVIDENCED BY X-RAYS IN INFANTS 4 TO 8 MONTHS OF AGE AT INITIAL EXAMINATION.

Feeding	Number of infants	Number premature infants	Rickets observed at initial examination.				Maximum rickets observed at any time after initial examination.				Rickets observed at final examination.			
			No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets	No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets	No rickets	Very slight rickets	Mild rickets	Moderate and marked rickets
No vitamin D	34	3	27	7	0	0	23	6	4	1	27	3	3	1
1 teaspoonful of cod liver oil	28	3	23	5	0	0	24	3	1	0	26	2	0	0
2 teaspoonfuls " " " "	30	4	22	8	0	0	25	3	2	0	29	1	0	0
3 " " " " " "	33	3	25	8	0	0	25	4	3	1	30	0	2	1
100 units of viosterol	20	1	17	3	0	0	18	2	0	0	18	2	0	0
200 " " " " " "	15	4	10	5	0	0	10	3	2	0	12	1	2	0
400 " " " " " "	19	3	15	4	0	0	15	4	0	0	19	0	0	0
800 " " " " " "	20	5	17	3	0	0	16	3	1	0	20	0	0	0
1 pint of vitamin D milk	33	8	28	5	0	0	27	3	3	0	32	0	1	0
Over 1 pint of vitamin D milk	61	8	49	12	0	0	54	6	1	0	60	0	1	0
Total	293	42	233	60	0	0	237	37	17	2	273	9	9	2

cases were eggs administered oftener than once every second day, and they were seldom given for a period longer than one and one-half months. The figures tabulated in Table XIV show that few infants in the groups under four months of age at the initial examination received egg yolk. Of the infants in the groups 4 to 8 months of age at the initial examination, 33 per cent received egg yolk. However, the administration of egg yolk was sufficiently evenly distributed amongst the groups that it is improbable that this factor alters the relative results.

In the various Tables will be found the number of infants which developed rickets as evidenced by x-rays under the three classifications—very slight rickets, mild rickets, and moderate and marked rickets. From the view-

point of the practising physician a comparison of the number of cases which developed moderate and marked rickets throughout the course of the observation is probably of the greatest interest. These cases of moderate and marked rickets are without question of clinical significance.

When Table V is examined a number of striking facts are evident. In the groups under 4 months of age at initial examination none of the 14 infants for whom 1 teaspoonful of cod liver oil daily had been prescribed developed moderate or marked rickets, while 1 out of 15 and 1 out of 17 developed moderate or marked rickets where 2 and 3 teaspoonfuls of cod liver oil was prescribed respectively. With the groups 4 to 8 months of age at initial examination receiving cod liver oil only 1 child de-

TABLE XII.
DISTRIBUTION OF BREAST AND BOTTLE FED INFANTS IN THE DIFFERENT GROUPS

	Infants under 4 months of age at initial examination.				Infants 4 to 8 months of age at initial examination.			
	Breast Milk		Cow's Milk		Breast Milk		Cow's Milk	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
No vitamin D	21	67	10	33	8	24	26	76
1 teaspoonful of cod liver oil daily	8	57	6	43	10	36	18	64
2 teaspoonfuls " " " " " "	6	40	9	60	5	17	25	83
3 " " " " " "	12	70	5	30	8	24	25	76
100 units of viosterol daily (Steenbock)	18	60	12	40	9	45	11	55
200 " " " " " "	20	70	9	30	3	20	12	80
400 " " " " " "	19	70	8	30	6	32	13	68
800 " " " " " "	12	46	14	54	6	30	14	70
1 pint (20 ounces) of irradiated milk daily	0	0	38	100	0	0	33	100
Over 1 pint of irradiated milk daily	0	0	9	100	0	0	61	100

TABLE XIII.
RATE OF GAIN IN WEIGHT OF INFANTS IN DIFFERENT GROUPS

	Under 4 months of age at initial examination.						4 to 8 months of age at initial examination.					
	Weight gain above normal		Weight gain normal		Weight gain below normal		Weight gain above normal		Weight gain normal		Weight gain below normal	
	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent	No.	Per cent
No vitamin D	17	55	8	26	6	19	11	32	16	47	7	21
1 teaspoonful of cod liver oil daily	6	43	7	50	1	7	10	36	10	36	8	29
2 teaspoonfuls " " " " "	6	40	7	47	2	13	13	43	13	43	4	13
3 " " " " " "	6	35	8	47	3	18	15	45	12	37	6	18
100 units of viosterol daily	11	37	14	46	5	17	7	35	12	60	1	5
200 " " " " "	10	35	15	51	4	14	10	66	4	27	1	7
400 " " " " "	8	30	17	63	2	7	12	63	4	21	3	16
800 " " " " "	9	34	12	46	5	20	11	55	7	35	2	10
1 pint (20 ounces) of irradiated milk daily	9	23	19	50	10	27	14	42	11	34	8	24
Over 1 pint of irradiated milk daily	1	11	5	55	3	33	26	43	23	37	12	20

veloped moderate or marked rickets, and for this infant 3 teaspoonfuls of cod liver oil daily had been prescribed. The results given in this Table show that the prescription of 1 teaspoonful of cod liver oil daily (130 Steenbock vitamin D units) was at least as efficacious in the prevention of rickets, as evidenced by x-rays of the forearms, as were 2 and 3 teaspoonfuls of cod liver oil.

The effectiveness of viosterol in the prevention of rickets is shown by Table VII. Out of a total of 112 infants under 4 months of age at the initial examination, and 74 infants 4 to 8 months of age at the initial examination, not a single infant developed moderate or marked rickets over a period of five months. It should be noted that prescriptions of 100, 200, 400 and 800 Steenbock vitamin D units of viosterol daily (1.5 to 12 drops of 250D viosterol) were equally efficacious in the prevention of moderate and marked rickets as evidenced by x-rays

of the forearms. The effectiveness of the administration of irradiated vitamin D milk in the prevention of rickets as evidenced by x-rays of the forearms is shown in Tables VIII and IX. The administration of 20 to 40 ounces daily of irradiated vitamin D milk over a period of five winter months to 141 Toronto infants, largely of British and northern European descent, 47 of whom were under 4 months of age at the initial examination, and 94 from 4 to 8 months, prevented the development of moderate or marked rickets, as shown by x-rays of the forearms, in every instance.

By applying standard statistical procedures one can determine the likelihood that the difference between any of the results obtained might be due to coincidence only and not to the experimental variant. For most biological work, if there is only one chance or less in twenty that the difference in the results being compared could be due to coincidence, it is safe

TABLE XIV.
INFANTS IN EACH GROUP WHO RECEIVED EGGS AT ANY TIME DURING PERIOD OF OBSERVATION

	Infants under 4 months of age at initial examination.		Infants 4 to 8 months of age at initial examination.		
	Total number of infants	Number receiving eggs	Total number of infants	Number receiving eggs	Per cent receiving eggs
No vitamin D	31	1	34	10	30
1 teaspoonful of cod liver oil daily	14	0	28	11	39
2 teaspoonfuls " " " " "	15	0	30	8	27
3 " " " " " "	17	1	33	9	27
100 units of viosterol daily (Steenbock)	30	1	20	6	30
200 " " " " "	29	5	15	6	40
400 " " " " "	27	3	19	5	26
800 " " " " "	26	2	20	9	45
1 pint (20 ounces) of irradiated milk daily	38	3	33	15	45
Over 1 pint of irradiated milk daily	9	2	61	19	31

to conclude that the difference is statistically significant. However, to be statistically certain, most authorities require the chances against coincidence to be at least 100 to 1.

In the results shown in Tables V, VII, VIII and IX, the figures have been subjected to such calculations.* Considering only moderate and marked rickets, in the older group of children the numbers are too small to have any positive significance; in the younger group the numbers are still small but are not all insignificant. For example, moderate and marked rickets is prevented by one pint of vitamin D milk, and the chances of this not being due to coincidence are 30 to 1. This result therefore is sound. The different doses of viosterol apparently prevent this degree of rickets, but as there is one chance in ten of their being due to coincidence, they are not conclusive when taken separately. If however any two of the groups receiving different amounts of viosterol be combined, the increase in the numbers involved makes the antirachitic action of the viosterol statistically certain. The cod liver oil in any or all doses gives no statistically significant result.

The cases which developed only to the degree of mild rickets, although of doubtful clinical interest, may be included in the statistical study of the comparative antirachitic potency of the various substances. When the cases developing mild rickets are combined with those with moderate and marked rickets in the infants under 4 months of age at the initial examination, the antirachitic action of the different amounts of viosterol, considered separately, is statistically significant. The antirachitic action of the different cod liver oil groups when considered together is also statistically significant, but when the cod liver oil groups are considered individually the results are not statistically sound. The results showing the antirachitic potency of 100 to 800 units of viosterol daily, and also the results showing the antirachitic potency of over 20 ounces of irradiated vitamin D milk are statistically significant. On the other hand, the figures showing the apparent rickets-preventing effect of 100 or 400 units of viosterol, when statistically analyzed, show that the chances of this apparent antirachitic effect being real and not merely due to coincidence are only 10 to 1.

* The authors are indebted to Dr. C. B. Weld for the statistical analysis.

The results of the cod liver oil groups in all or any doses, of the 200 or 800 viosterol units groups when considered individually, and also of the 20 ounces irradiated vitamin D milk group, fail to show statistically any significant antirachitic potency.

We would like to point out that in our observation, as was also shown by Hess and Lewis,⁴ 35 units of vitamin D in the form of vitamin D milk were as efficacious as 800 units of viosterol. However, the further observation is made that 100 units of viosterol are just as efficacious as 800 units. Whether further reduction in the units of viosterol administered might show that only 35 units of viosterol were equivalent to 35 units of vitamin D in the form of irradiated milk, we cannot say at present.

Recent editorials in the leading medical journals of Great Britain and the United States have commented on the discouraging fact that in spite of constant effort to emphasize the need for the routine administration of some antirachitic material to infants and young children rickets is still quite prevalent. We believe that the great value of irradiated vitamin D milk lies in the automatic and regular administration of vitamin D when given in this manner. However, because the young infant is more susceptible to rickets than the older infant or child, and taking into consideration the fact that the small infant consumes less milk, and consequently less vitamin D, we feel it is desirable during the early months of life to supplement the vitamin D administered in the form of vitamin D milk with some other antirachitic substance.

SUMMARY

1. A study of the antirachitic value of cod liver oil, viosterol and irradiated vitamin D milk on 529 Toronto infants, largely of British and northern European descent, was made under home conditions over a period of five winter months. The ages of the infants at the initial examination varied from 3 weeks to 8 months.

2. At the present time when a large group of infants is being studied, x-ray examination is our best means for the diagnosis of rickets, and reliance cannot be placed on the usually accepted clinical signs, namely, craniotabes, rosary, or moderate enlargement of the epiphyses.

3. Toronto sunshine, as at present used, is not entirely efficacious in preventing x-ray evi-

dence of rickets, since 12.8 per cent of 349 infants examined in October showed very slight rickets, and 4.5, mild rickets. No infants however showed moderate or marked rickets.

4. Infants under 4 months of age in October are more apt to develop rickets in the succeeding five winter months than are infants from 4 to 8 months of age in October.

5. One, 2 or 3 teaspoonfuls of cod liver oil were prescribed for 137 Toronto infants, largely of British or northern European descent. Three infants developed moderate or marked rickets during a period of five winter months. Difficulties encountered in the administration of cod liver oil under home conditions may have accounted for the development of rickets in these infants.

6. One teaspoonful of cod liver oil was at least as efficacious as 3 teaspoonfuls in the prevention of rickets, as evidenced by x-rays.

7. One hundred, 200, 400 and 800 Steenbock vitamin D units, in the form of viosterol (1.5 to 12 drops of 250D viosterol), were prescribed for 186 Toronto infants, largely of British or northern European descent. Under these conditions no infants developed moderate or marked rickets during a period of five winter months.

8. One hundred, 200, 400 and 800 units, in the form of viosterol (from 1.5 to 12 drops of 250D viosterol), were efficacious to the same degree in the prevention of rickets, as evidenced by x-rays.

9. From 20 to 40 ounces of irradiated vitamin D milk, containing 35 Steenbock vitamin D units per 20 ounces, were prescribed to 141 Toronto infants ranging in age at initial examination from 3 weeks to 8 months, and largely of British or northern European descent. The milk was administered over a period of five winter months. Under these conditions no infants developed moderate or marked rickets.

10. In irradiated vitamin D milk we have a valuable addition to our present anti-rachitic armamentarium.

We desire to express our appreciation of the co-operation and assistance given us by Dr. Gordon Jackson, Medical Officer of Health, City of Toronto. We also wish to thank the various physicians in the well baby clinics who have cooperated so splendidly in this work.

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A CONVENIENT METHOD FOR DETERMINING SERUM AND BILE PHOSPHATASE ACTIVITY*

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CLINICAL laboratories are at the present time frequently being called upon to make estimations of the phosphatase activity of blood serum. This demand has followed upon the realization of the diagnostic aid which such a determination may lend in cases of both bone disease (Kay;^{6,7} Roberts⁹) and jaundice (Roberts;¹⁰ Armstrong, King and Harris¹).

Robison¹¹ described the presence of phosphatase in bone and ossifying cartilage and in blood (Robison, Hansman and Martland¹²) and outlined a method for determining the relative enzyme content of a solution. While considerable progress has been made since then in diminishing the time required for such a deter-

mination, present methods are as yet too time-consuming and laborious for clinical work.

Since the enzyme has not been obtained in a pure state, the amount present in a given solution is expressed in terms of its ability to effect hydrolysis on a given substrate. Such ability is known as phosphatase activity and is expressed in arbitrary units.

The fundamental basis of determining phosphatase activity has been the same in all methods to date. It has consisted in measuring the phosphorus set free as inorganic phosphate when the enzyme is allowed to act on a substrate (disodium B glycerophosphate) under standard conditions. An example of a representative method adapted to clinical needs is that of Jenner and Kay.⁵ Using the procedure of these

* Received for publication June 6, 1934.

authors, 5 c.c. of blood are required from the patient to supply enough plasma for duplicate analyses. The time required for a complete determination is about 5 hours, and the accuracy is well beyond that required clinically. Similar procedures, in which the hydrolysis has been conducted over shorter intervals, have been described by Roberts⁹ and by Bodansky.³ Unfortunately, the units of phosphatase activity adopted by the different authors have not been the same. Thus the results reported, which comprise a large and valuable series, cannot readily be compared.

The objects in view when the present study was commenced were three: firstly, to elaborate a more rapid and, if possible, more accurate method than those previously described; secondly, to limit the total amount of serum required for duplicate test and control hydrolysis to 2 c.c.; and, thirdly, to express the relative amount of phosphatase found in units numerically equal to those of Jenner and Kay.* Fortunately, by employing a different substrate it has been found possible to fulfil all three objects set forth above. The new unit represents almost exactly the same amount of enzyme as the former one. The definition of that unit is, however, entirely different.

King⁸ observed that the rate at which di-sodium phenyl phosphate is hydrolyzed by phosphatase was approximately double the rate for di-sodium B glycerophosphate. Theoretically, therefore, by substituting the former substrate for the latter in the Jenner and Kay method, the time required for hydrolysis could be reduced to about one and a half hours. The time of hydrolysis was further reduced by taking advantage of the fact that the estimation of the phenol liberated gives the same measure of the extent of hydrolysis as does the estimation of the liberated phosphate. In a given weight of phenyl phosphate there is approximately three times as much phenol, weight for weight, as there is phosphorus, so that after a hydrolysis lasting 30 minutes there would be as much phenol liberated by weight as there would be phosphorus at the end of one and a half hours. Hence, if small amounts of phenol could be measured with the same degree of accuracy as

similar amounts of phosphorus, then the time for hydrolysis in the above substitution could be limited to 30 minutes. Fortunately, an accurate procedure for estimating phenol was available.

The phenol method of Benedict and Theis² was tried out, since it offers the advantage of being fairly specific and the reagent is easily prepared. However, the colours were difficult to read in the colorimeter and turbidities were troublesome. Folin and Ciocalteu⁴ described a reagent (a phosphotungstic phosphomolybdic acid) for determining tryptophane and tyrosine in blood, which forms a blue colour with phenol when made alkaline. This reagent, although it takes some time to prepare, was found to be very adaptable to our purpose, and it possesses the advantage of being a good protein precipitant. The colours can be read with great ease in the colorimeter and turbidities do not develop. It was finally adopted after some necessary modifications.

The cumbersome use of the several substances required for glycine-sodium hydroxide-sodium chloride buffer was avoided by the use of the veronal buffer of Michaelis. Jenner and Kay had avoided this buffer since they had trouble with crystallization when the solution was acidified. Bodansky³ claimed never to have had this experience. However, his buffer solution is so weak that it must be handled with great care and kept under a layer of paraffin, lest carbon dioxide from the air lower the pH. Employing a much stronger veronal solution, we have found that the pH of the buffer solution thus prepared is remarkably constant. Some of the samples of veronal tested have crystallized out when made faintly acid; others have not. The cause for this we do not know, but it is easy to secure a suitable sample and then make further purchases of material made in the same batch.

For the sake of convenience both buffer and substrate are made up in one solution and preserved with a few drops of chloroform in the ice-chest. If there is any suspicion that hydrolysis may have occurred in the solution after standing, this point may be briefly settled by adding to a few c.c. of it a little of the phenol reagent and making it alkaline. Only a trace of blue colour should develop.

Serum and oxalated plasma were employed interchangeably, since we found that there were no appreciable differences in the results ob-

* One Jenner and Kay unit represents that amount of enzyme which will liberate one mg. of phosphorus as free phosphate from an excess of di-sodium B glycerophosphate at pH 8.8 in 3 hours, when kept at a temperature of 37.5° C.

tained. Bodansky (1933) also employed serum in preference to plasma.

Under the conditions of the test employed, 1 unit of phosphatase is that amount of enzyme which, when allowed to act upon excess disodium phenylphosphate at pH 9.0 for 30 minutes at 37.5° C., will liberate 1 mg. phenol.

SOLUTIONS REQUIRED

1. *Buffer Substrate*.—Molar/200 phenyl phosphate in molar/20 veronal.

10.3 g. sodium veronal.

1.09 g. di-sodium phenylphosphate.*

Water to 1 litre.

Preserve in a well-stoppered bottle with a few drops of chloroform, and keep in the ice-chest when not in use. (This solution keeps at least 1 month).

2. *Phenol Reagent of Folin and Ciocalteu*.†—As described in Peters and Van Slyke "Quantitative Clinical Chemistry", 2: 655, and in Hawk and Bergeim, 10th Edition, p. 866.

Dilute this reagent 1 in 3.

3. *20% solution of sodium carbonate (Na₂CO₃)*.

4. *Stock Standard Phenol (approximately 100 mg. per 100 c.c. solution of phenol)*.—Dissolve 1 g. crystalline phenol in 0.1 N HCl and make up to 1 litre with 0.1 N HCl. Titrate with iodine as described in Peters and Van Slyke, "Quantitative Clinical Chemistry", 2: 655, and in Hawk and Bergeim, 10th Edition, p. 866, and note the exact strength. (This solution keeps indefinitely).

5. *Diluted Stock Standard Phenol (exactly 10 mg. per 100 c.c. solution of phenol)*.—Made by a suitable dilution of (4). (This keeps at least 3 months in the ice-box).

6. *Standard phenol solution and reagent (1 mg. phenol per 100 c.c.)*.—

5 c.c. diluted stock standard (10 mg. per 100 c.c.).

15 c.c. diluted phenol reagent.

Water to 50 c.c.

(Make up daily).

PROCEDURE

Blood.—Five c.c. of blood are drawn from an arm vein in the usual manner and without the addition of anti-coagulant. After the clot has formed it is loosened from the sides of the tube and then centrifuged. The serum is poured off into a centrifuge tube, and after being again well centrifuged to get rid of any suspended cells is ready for use. If the determination cannot be done on the day the blood is taken, the blood should be preserved in the ice-box over night. The results obtained on sera before and after 24 hours' preservation in the ice-box agree very closely.

Test.—In 2 test tubes place 10 c.c. of buffer substrate. Allow the tubes to remain in a water bath at 37.5° C. for 5 minutes or more. Without removing the tubes from the bath, add

exactly 0.5 c.c. serum to each, stopper, mix, and allow to remain in the bath exactly 30 minutes. At the end of this time add at once 4.5 c.c. of dilute phenol reagent, mix, and filter.

Control.—In 2 test tubes place 10 c.c. buffer substrate. Add to each 0.5 c.c. serum and at once 4.5 c.c. diluted phenol reagent and filter. Pipette 10 c.c. filtrate from the test and control solutions into clean test tubes. Add 2.5 c.c. of 20 per cent sodium carbonate, mix, and replace tubes in the water bath for five minutes to bring up the colour.

Comparison.—Compare in the colorimeter with a standard made up at the same time by taking 10 c.c. of standard phenol solution and reagent (No. 6 above), and 2.5 c.c. of 20 per cent sodium carbonate. Place the unknown solution on the left side of the colorimeter, and set at 30 mm. Place the standard on the right side and match the colours.

Calculation.—The phosphatase activity of a serum is expressed as units per 100 c.c. of serum and is numerically equal to the mg. of phenol which would be set free from the phenyl phosphate under the standard conditions by 100 c.c. of serum. Thus:

$$\begin{array}{ccc} \text{Units of phosphatase per 100 c.c.} = & & \\ \frac{\text{mg. phenol per 100 c.c.}}{\text{serum in test}} & = & \frac{\text{mg. phenol per 100 c.c.}}{\text{serum in control}} \end{array}$$

The number of mg. phenol in 100 c.c. of serum in the test and in the control is found by the equation:

$$\frac{\text{Reading of Standard} \times \text{Strength of Standard} \times 15 \times 100}{\text{Reading of Unknown} \times 10 \times 0.5}$$

With the unknown solution set at 30 mm. and the strength of standard = 0.1 mg. this equation can be written:

$$\frac{\text{Reading of Standard} \times 0.1 \times 15 \times 100}{30 \times 10 \times 0.5}$$

All figures in the above equation cancel out, making it equal to "Reading of Standard".

More simply, then:

$$\begin{array}{ccc} \text{Units of phosphatase per 100 c.c.} = & & \\ \frac{\text{Reading of Standard}}{\text{(against the Test)}} & = & \frac{\text{Reading of Standard}}{\text{(against the Control)}} \end{array}$$

Procedure when the enzyme content of the serum is very high.—So long as the enzyme content of the serum is less than 30 units the colorimetric reading is carried out as described above. If more than 30 units are present, but less than

* Di-sodium-monophenylphosphate may be purchased from British Drug Houses, Limited.

† Phenol Reagent of Folin and Ciocalteu may be purchased from the J. F. Hartz Company, Toronto.

60 units, the reading of the unknown for the test solution should be set at 15 mm. In such a case "Reading of Standard" (against test) must then be multiplied by 2 to obtain mg. phenol per 100 c.c. of serum. When the enzyme content of serum is very high, the products of hydrolysis will become correspondingly greater in amount. These, especially the phosphate, have a retarding influence on the velocity of the hydrolysis when a certain concentration is reached. By experimentation we have found that if less than 60 units of phosphatase are present dilution of the serum yields the same final result as is obtained in the undiluted serum. However, if the serum contains above 100 units very great differences are found between diluted and undiluted serum. Two such experiments gave the following results.

	Case 1	Case 2
Undiluted	123 units	118 units
Diluted with inactivated serum		
1 to 3	202 "	170 "
1 to 9	199 "	165 "
" " saline 1 to 3	206 "	183 "

For routine work it is our custom to dilute high phosphatase sera with normal saline, so that the number of units per 100 c.c. of diluted serum will not be in excess of 60.

The pH of the buffer substrate colorimetrically by B.D.H. capillator = 9.6 at room temperature. After addition of serum the pH = 9.3 - 9.5, (checked by potentiometric measurement). The actual pH at 37.5° C. would thus be pH 8.9 - 9.1.

THE ACCURACY OF THE METHOD

The 30 minute incubation period as used in this method is of advantage in that it gives results which more truly represent the actual enzyme content of the blood than is the case with methods requiring a longer period of incubation. Theoretically, a proper measurement of the amount of the enzyme should be based on the initial velocity of hydrolysis. While the attainment of this ideal condition is not practicable in a clinical method, the shortening of the period of hydrolysis, without any sacrifice in the accuracy of the analytical procedures, should make for the attainment of more exact and hence more significant values.

When large numbers of sera are being examined routinely we have found duplicate analyses to agree on the average to within 5 per cent for those values lying within the normal range. By exercising more care this

error can be cut down very considerably. For the higher values the percentage error is correspondingly less. (For the results of a series of consecutive cases see Table I).

TABLE I.

CONSECUTIVE SERIES OF CASES EXAMINED OVER A PERIOD OF TWO WEEKS SHOWING CLOSE AGREEMENT OF DUPLICATES. (ARRANGED IN ORDER OF ACTIVITY.)

No.	Control (zero time)			Test (30 minutes incubation)			Units		
	(1)	(2)	Difference	(1)	(2)	Difference	(1)	(2)	Difference
1	7.5	7.5	0	10.9	10.7	0.2	3.4	3.2	0.2
2	7.1	7.1	0	11.4	11.4	0	4.3	4.3	0
3	7.1	6.9	0.2	12.5	11.6	0.9	5.4	4.7	0.7
4	7.5	7.5	0	12.9	12.5	0.4	5.4	5.0	0.4
5	6.8	7.1	0.3	12.9	12.5	0.4	6.1	5.4	0.7
6	6.4	6.2	0.2	13.0	12.9	0.1	6.6	6.7	0.1
7	7.2	7.2	0	13.2	13.8	0.6	6.0	6.6	0.4
8	6.4	6.2	0.2	14.1	13.9	0.2	7.7	7.7	0
9	6.9	7.1	0.2	15.5	15.4	0.1	8.6	8.3	0.3
10	7.3	7.6	0.3	15.6	15.9	0.3	8.3	8.3	0
11	7.4	7.4	0	16.6	16.7	0.1	9.2	9.3	0.1
12	7.4	7.4	0	16.7	19.7	3.0	9.3	12.3	3.0
13	6.6	6.5	0.1	18.1	18.6	0.5	11.5	12.1	0.6
14	7.5	7.5	0	19.0	18.6	0.4	11.5	11.1	0.4
15	7.9	7.5	0.4	20.3	21.3	1.0	12.4	13.8	1.4
16	7.7	7.7	0	20.6	19.5	1.1	12.9	11.8	1.1
17	7.5	7.7	0.2	22.9	22.7	0.2	15.4	15.0	0.4
18	7.6	7.7	0.1	23.3	23.4	0.1	15.7	15.7	0
19	7.2	7.2	0	24.5	25.0	0.5	17.3	17.8	0.5
20	9.4	9.2	0.2	25.0	25.0	0	15.6	15.8	0.2
21	7.3	7.4	0.1	25.3	24.9	0.4	18.0	17.5	0.5
22	5.8	5.9	0.1	25.5	24.7	0.8	19.7	18.8	0.9
23	9.5	9.7	0.2	35.1	35.3	0.2	25.6	25.6	0
24	8.9	8.9	0	35.4	35.9	0.5	26.5	27.0	0.5
25	8.3	8.1	0.2	38.3	38.4	0.1	30.0	30.3	0.3
26	7.5	7.7	0.2	47.2	46.4	0.8	39.7	38.7	1.0
27	6.3	6.3	0	73.6	73.6	0	67.3	67.3	0
28	8.9	9.1	0.2	89.4	90.3	0.9	80.5	81.3	0.8
29	5.9	5.7	0.2	92.1	91.5	0.6	86.2	85.8	0.4
30	6.0	6.0	0	96.6	95.1	1.5	90.6	89.1	1.7
31	8.9	8.9	0	119.7	119.7	0	110.8	110.8	0

TABLE II.

COMPARISON OF UNITS OF NEW METHOD WITH THOSE OF JENNER AND KAY

No.	Source of Serum	Jenner and Kay	New Method	Difference
1	Dog (2)	3.1	6.0	+2.9
2	Rabbit (p)	5.9	6.7	+0.8
3	Dog (A)	6.1	7.4	+1.3
4	Rabbit (2)	6.1	6.9	+0.8
5	" (3)	6.4	9.3	+2.9
6	Human (P)	6.5	8.0	+1.5
7	" (A)	6.8	6.8	+0.0
8	Dog (p)	6.8	7.4	+0.6
9	Rabbit (1)	6.9	8.5	+1.6
10	Human (M)	8.6	9.1	+0.5
11	" (O)	9.2	9.4	+0.2
12	Sheep	9.2	11.3	+2.2
13	Dog (1)	9.3	9.8	+0.5
14	Human (1)	9.7	10.0	+0.3
15	" (R)	9.7	9.5	-0.2
16	" (J)	12.8	12.5	-0.3
17	Dog (3)	14.4	13.3	-1.1
18	Human (B)	17.7	19.7	+2.0
19	" (A)	29.0	26.6	-2.4

A number of sera were examined simultaneously by our own method and by that of Jenner and Kay (Table II). Between the values of 3 to 30 the two methods agree very closely, and most of the differences are scarcely beyond the combined experimental error of both methods. If the serum is diluted before analysis there is considerable divergence. In such cases the new method gives distinctly higher values. The cause for this has not been fully investigated, but addition of Mg.++ ions to both our substrate and to Jenner and Kay's leads to a marked lessening of this difference.

RANGE OF THE NORMAL IN THE NEW METHOD

The range of units of serum phosphatase found by the new method in 24 apparently healthy laboratory workers is presented in Table III. The ages range from 19 to 42 years. All values lie between 3.7 and 13.1 units; the great majority lie between 5 and 10 units. There is no obvious difference between males and females. Estimations repeated on individuals on different

TABLE III.

SERUM PHOSPHATASE IN HEALTHY LABORATORY WORKERS AND APPARENTLY HEALTHY LABORATORY ANIMALS

No.	Initial	Age	Sex	Units of Phosphatase	No.	Initial	Age	Sex	Units of Phosphatase
1	M.D.	24	F	3.7	14	H.P.	29	M	8.0
2	H.T.	24	F	4.8	15	G.M.	19	F	8.0
3	H.E.	37	M	5.4	16	F.N.	32	M	8.2
1A	M.D.	24	F	5.5	17	E.K.	32	M	8.2
4	G.C.	40	M	5.8	18	G.O.	30	M	8.3
5	L.P.	26	M	5.9	17A	E.K.	32	M	8.9
6	K.W.	24	M	6.0	19	M.M.	28	M	9.1
7	W.F.	33	M	6.0	20	F.B.	42	M	9.2
8	M.W.	24	F	6.1	18A	G.O.	30	M	9.4
6A	K.W.	24	M	6.5	21	J.R.	31	M	9.5
9	B.B.	27	M	6.6	22	D.I.	34	M	10.0
10	R.A.	29	M	6.8	23	J.F.	34	M	10.0
11	E.H.	26	M	7.0	5A	L.P.	26	M	11.1
12	A.S.	28	F	7.3	24	E.B.	24	F	11.7
13	A.M.	27	M	7.7	23A	J.F.	34	M	13.1
1	Dog			1.9	11	Dog			7.4
2	"			2.3	12	"			9.0
3	"			2.4	13	"			9.8
4	"			3.4	14	"			10.1
5	"			4.5	15	"			10.4
6	"			4.6	16	"			10.9
7	"			4.7	17	"			11.5
8	"			5.6	18	"			13.3
9	"			6.0	19	"			15.7
10	"			6.6	20	"			27.4
					21	"			32.1
Sheep				11.3					
1	Rabbit			6.9					
2	"			8.5					
3	"			9.3					

occasions (indicated by letter A) showed little change beyond that to be expected due to experimental error in the low range. On the basis of these findings it would seem advisable to look with suspicion upon any values below 3.0 units or above 13.0 units. The estimations made on dog sera indicated a somewhat wider range of values than was found in the human cases. Two of the twenty-one dogs (No. 20 and No. 21) presented remarkably high values—too high, perhaps, to be regarded as normal. However, we were unable to detect any abnormality which might account for this, and thus have included them in the Table. The sheep and the rabbits examined had values well within the range given for human beings.

TABLE IV.

SERUM PHOSPHATASE IN VARIOUS CLINICAL CONDITIONS

Case No.	Diagnosis	Serum Phosphatase
1	Latent parathyroid tetany	6.9
2	Active parathyroid tetany	7.0
3	Fractured femur	12.1
4	Pott's fracture	10.7
5	Fragilitas ossium	23.3
6	Multiple myelomata	14.9
7	Hyperparathyroidism—Rarefaction of bones	67.5
	(1 month later)	121.0
8	Fibrocystic disease	110.0
9	Cholecystitis and cholelithiasis without obstruction	28.8
10	Infectious jaundice	36.7
11	Obstructive jaundice	65.0
12	Obstructive jaundice	162.0
13	Acute hemorrhagic pancreatitis	6.5
14	Baby, aged 28 months; convalescent from pneumonia	19.0
15	Baby, aged 9 months; scurvy	23.0
16	Baby, aged 12 months; craniotabes	90.0
17	Baby, aged 16 months; burns on hands	18.0

ADAPTABILITY OF METHOD TO THE ESTIMATION OF PHOSPHATASE IN BILE

Several investigators have attempted to measure the activity of the enzyme in bile and have not been very successful. The new method lends itself readily to this purpose.

Procedure.—Dilute the bile 1:10 and 1:100 with normal saline. Treat the diluted bile as serum in the method described for serum. Two dilutions of the bile are necessary, since some biles contain enormous activity (7,000 units per 100 c.c.). A discussion of this is, however, reserved for a future paper.

SUMMARY

1. A new method is described for estimating serum phosphatase activity in which the enzyme is allowed to act on phenyl phosphate and the liberated phenol is determined.
2. The method is adaptable for use with bile.
3. The time required for duplicate analysis of a serum is about one hour.
4. The accuracy of the method is considered to be as great as or greater than that of previously described methods.
5. The procedure is simple, and only the ordinary glassware found in a clinical laboratory is required.
6. The unit by this method is almost the same numerically as that of Jenner and Kay.

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THE DIFFERENTIAL DIAGNOSIS OF COMA

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A GENERATION or so ago therapeutics had little to offer in cases of coma but nursing and waiting. Diagnosis, although highly desirable, was not urgently needed. Since then the discovery of insulin and the rapid development of brain surgery have introduced new methods of treatment, and early and accurate diagnosis has assumed new importance. Perhaps this may be considered sufficient excuse for reviewing the subject of the differential diagnosis of coma.

For the present purpose coma may be defined broadly as a loss of consciousness, more or less profound, transient or prolonged; excepting only the physiological condition of sleep. Whatever may be said about the nature of mental processes and mental awareness, both of these are associated with the activity of cerebral cells, and during coma the function of at least some of these cells is in abeyance. We know that this loss of function may occur from various causes.

1. *Cerebral anæmia*.—It is probable that, fundamentally, cerebral anæmia is the cause of most cases of sudden coma, since interference with cerebral circulation may be brought about in various ways, such as remote or local hæmorrhage, vasomotor disturbance, cerebral œdema, or compression from trauma. Familiar examples of the *obvious* cases of cerebral anæmia are vaso-

vagal syncope, as in fainting, and serious external or internal hæmorrhage remote from the brain itself. To be effective in producing coma severe extracranial loss of blood must be sudden, because nature may acquire a tolerance for an extreme degree of anæmia if she has sufficient time.

2. *Mechanical injury of the brain*.—This may produce coma, even if it is so slight as to cause nothing more than concussion, with little or no pathological lesion so far as we know.

3. *Convulsive attacks*.—Coma, generally of short duration, follows epileptic seizures. It may be noted that a recent text-book has enumerated forty-eight other causes of fits beside epilepsy. The diagnosis of epilepsy without a history may therefore require a good deal of exclusion.

4. *Cerebral vascular accidents*.—Such as hæmorrhage, thrombosis and embolism.

5. *Poisons*.—(a) *Exogenous agents*, inhaled, ingested or injected. A few of these, e.g., carbon monoxide, may act with great rapidity; others, as in chronic lead poisoning, may produce coma after months or years of exposure. (b) *Endogenous toxic products*.—These are conveniently subdivided into the toxæmias associated with acute infection like typhoid fever, and those cases arising from disturbed metabolism, as in

diabetes, hypoglycæmia, uræmia, eclampsia and cholæmia.

6. *Local infection of brain and meninges.*—This does not exhaust the list by any means.

There are other causes of coma which are difficult to classify. Hysteria has not been included; probably the state of apparent unconsciousness found in this condition is not coma at all. Sun-stroke could be put in the group of disturbed metabolism, if, as some think, it may be due to diminution of alkaline reserve and accumulation of lactic acid in the body. The list is large enough, however, to indicate that the differential diagnosis of coma offers a wide field of possibilities.

The problem may be approached with some general observations, remembering, of course, that generalities are subject to exceptions. In the first place we should always beware of the obvious. A man has a stroke and falls off a ladder. What more natural than to attribute the coma to the head injury which is found. A well known alcoholic is found unconscious on the sidewalk in front of his house. He smells strongly of whiskey, but close examination of his head reveals a fracture of the skull. Later it is learned that he had been inspecting an unfinished house two miles away and there is evidence that he had fallen, but apparently without serious injury. A man was found partly dressed lying across his bed in a state of coma from which he died a few minutes later. As he smelled strongly of carbolic acid his daughter thought he had committed suicide. Investigation clearly indicated that he had been taken ill while dressing and had gone to the bathroom to get a drink. There he had picked up a glass which contained a carbolic mouth wash. It slipped out of his hands, the contents drenching his clothes, and crashed on the floor. The man managed to get back to his room and fell unconscious on the bed. Autopsy showed that he had died of coronary thrombosis. The moral of all this is that thorough examination and investigation are necessary, no matter what the circumstances are.

The possibilities are at once reduced if one can find definite evidence of an intracranial lesion. The history may suggest this, but the proof rests on examination with three questions in mind.

1. *Is there one clear-cut abnormal unilateral sign on investigation of the nervous system?*

Practically this applies to cranial nerve disturbance, reflexes, and muscular paralysis, flaccidity, or hypertonicity. Here it must be remembered that previously existing lesions may leave their mark on the nervous system. For example, permanent changes in reflexes may remain after an illness involving the anterior horn cells or peripheral nerves.

2. *Is there increased intracranial pressure?*

While there may be considerable evidence in favour of this, derived from history and examination, the most important finding is optic papilloedema. The explanation is clear. The subarachnoid space around the brain is continued along the optic nerve as it passes into the orbit. For this reason cerebrospinal fluid under unusual tension will generally be indicated by œdema of the optic disk. This condition may be recognized, at least where it is marked, by any general practitioner without any training except that derived from his own personal experience. It is merely a matter of using an ophthalmoscope often enough in normal cases to detect changes when they occur. Once he has got that far he will not be satisfied until he can put some interpretation on the abnormal things he sees.

3. *Are there signs of meningeal irritation?*

These are much more in evidence when the patient is conscious, but, generally, even in coma, cervical rigidity, spinal stiffness and the Kernig sign may persist. The last should not be accepted in adults unless difficulty is encountered in straightening the knee before the right angle is reached.

In the investigation of coma, as in other abnormal conditions, the terminology of nervous diseases has certain disadvantages. We are prone to grope at once for a designatory name. Obviously, signs and symptoms should be interpreted as far as possible in terms of impaired function of this or that part of the body; they do not stand for this or the other disease. For example, a slow respiratory rate does not necessarily indicate a brain tumour. It merely means that something has gone wrong with the respiratory centres. A positive Babinski sign does not do any more than tell us that for some reason or other the controlling influence of the upper neurones is in abeyance.

The cause of coma is often known before it begins. The difficulty arises when the patient is comatose when first seen, or where he has been

suffering from an obscure illness before. The history may give some clue, but examination is much more certain in its results. In view of the importance of discovering quickly those conditions which are amenable to treatment we may begin with what might be called an *emergency examination*, leaving the more systematic investigation until later.

Examination of the head for signs of injury comes first. If any are found, or if there is any doubt, the skull should be x-rayed if possible. It is imperative, *i.e.*, where head injury is found or suspected, that the patient be seen repeatedly during the first twenty-four hours at least, in order to determine whether there are changes in the pulse and respiratory rate, and especially whether blood pressure is rising rapidly. An increase in blood pressure in such a case is a compensatory change to improve circulation in a brain which is being compressed. Intracranial hæmorrhage is probably the answer, and it may be amenable to surgical treatment, especially if localizing signs indicate that the bleeding is coming from a torn middle meningeal artery. Much more easy to miss is the subdural hæmatoma which gradually forms and produces coma weeks or even months after what may have appeared to be a trivial head injury. In fact the latter may have been overlooked entirely, as the following case will show.

A man, 63 years old, was badly bruised about the shoulders and back in an automobile accident. There was no noticeable head injury. Some weeks later he began to have headache which gradually increased, with, however, occasional remissions. Still later he became confused, drowsy and finally comatose. Autopsy revealed a subdural hæmatoma, but surgery might have saved the man's life if the condition had been recognized early enough.

The question of poisoning must be settled at once. Usually the history and the circumstances will be of great value. A lead may be found in the previous mental state of the patient. Certain pictures of drug poisoning are unmistakable. The discoloration of mouth, hands or clothes is characteristic enough of corrosives. The pin-point pupils and the respiratory rate of less than twelve per minute indicate opium poisoning. As for many other poisons producing coma the signs are not so definite. In the last few years pharmaceutical research has led to the discovery of several new drugs which people with suicidal intent may use. At least, these drugs may be taken in overdoses in a desperate attempt to produce

sleep. Luminal and nembutal are in this category. Rarely coma supervenes in chronic lead poisoning, but one is not likely to overlook the history of exposure and the pigment line on the gums.

Having excluded injury and poisoning we face a question which may be urgent and sometimes difficult. Is the coma due to an endogenous toxic product? The cases arising from the profound toxæmia of infections, as a rule offer no difficulty, although it must be remembered that cerebral lesions may supervene in these patients and, on the other hand, that diabetic coma may be precipitated by even a mild infection. It should also be noted that hæmorrhage into the pons may be associated with a high temperature and might therefore be mistaken for infection.

The coma produced by grave metabolic disturbance may require careful investigation before a diagnosis can be made. Eclampsia needs no comment here. Cholæmia can scarcely be mistaken for anything else. Coma from hypoglycæmia rarely occurs except in patients taking insulin, but it may be the result of excessive production of insulin, as in tumour of the pancreas. If so, the diagnosis may easily be made by a blood sugar estimation.

Uræmia is often diagnosed when it does not exist. The mistake is due to the fact that too much importance has been given to the urinalysis. Albumin and casts will be found in many elderly people and in cases of hypertension, but these findings alone do not indicate that there is sufficient renal impairment to cause uræmia. Albuminuria is almost invariably found after a convulsive seizure, no matter what its cause may be. Albuminuria may be even massive in some cases of subarachnoid hæmorrhage. People known to have chronic nephritis may have cerebral vascular accidents *because* of the associated renal disease. Nor is coma in acute nephritis due necessarily to uræmia. It is probably the result of acute cerebral œdema. A urinary odour in the breath is highly suggestive, but where there is doubt a blood examination is required. The diagnosis of uræmia may be made only if the non-protein nitrogen is above 120 mg. or the urea nitrogen is above 80 mg. per 100 c.c. of blood.

In diabetes mellitus coma does not appear without warning. If coma occurs suddenly in a patient who has this disease the probability

is that a cerebral hæmorrhage has occurred as the result of the vascular changes which so often exist in long standing cases. The diagnosis of diabetic coma does not rest on the finding of sugar in the urine. Glycosuria is found again and again in coma due to head injury and to lesions in the pituitary or hypothalamic region. It is only when the urine is strongly positive for the ketone bodies, acetone and diacetic acid, and contains a large amount of sugar that the diagnosis of diabetic coma can be safely made. A definite odour of acetone in the breath is a valuable sign of ketosis. Once recognized, it is remembered well. Treatment will not wait for the confirmation of a blood sugar estimation. Where it can be done quickly, a reading of 0.2 per cent or over will clinch the diagnosis.

Almost at the beginning of investigation it will be possible to decide the question as to whether the coma is due to sudden cerebral anæmia from extracranial hæmorrhage. Coma from this cause is generally of short duration, and even internal hæmorrhage offers no difficulty. Coma may come as a terminal event in pernicious anæmia and leukæmia, and in these cases may be due to cerebral hæmorrhage, but the history and the bedridden patient are enough to prevent a mistake. There is one form, however, of cerebral anæmia in which the cause might be overlooked, *viz.*, the Stokes-Adams syndrome arising from complete or, more often, partial heart-block. The diagnosis can be made at once if the pulse at the wrist is forty or less and an auricular pulse of double or treble this rate can be seen in the veins of the neck.

If a patient is seen for the first time when he is in coma and no history is available it may be difficult to say whether it was preceded by a convulsive seizure. A bitten tongue or incontinence of urine may answer the question, but just as important is the soiling or disarrangement of the clothing by violent movement on the ground or floor. Scarring of the tongue will point to former seizures, and so make it probable that the case is one of epilepsy, but further investigation may be necessary to rule out the other forty-eight causes of fits.

Having excluded more particularly the conditions which are urgent from the standpoint of immediate treatment, the diagnosis narrows down to non-traumatic vascular lesions of the

brain and infections of the brain and meninges. Both require a more systematic examination than has been outlined, although they are easily differentiated by the history which is always available in infective conditions. Certain observations will have been made already, no matter how hurried the examination has been. The depth of the coma has been determined by an attempt to rouse the patient by voice or painful stimuli. The latter can be given in an unobtrusive way by sharply flexing the terminal phalanx of the little finger. If the arm on that side happens to be paralyzed there will be a defensive movement on the other side if the coma is not too deep. Changes in colour will have been noted, with some provisional interpretation. Disturbance of respiratory centres is common in all cases. Deep and exaggerated breathing without cyanosis suggests the presence of ketosis. The combination of florid, cyanotic face and stertorous breathing points to apoplexy. A slow pulse rate suggests an intracranial lesion. Both the respiratory and pulse rates may be slow with increased intracranial pressure, but both may go up later. A high blood pressure found early in coma probably existed before the attack, as in essential hypertension or chronic nephritis, but it may be recent and indicate a rising intracranial pressure. Cardiac enlargement and peripheral vascular changes will be noted. The absence of auricular fibrillation, coronary occlusion, mitral stenosis or other gross heart lesion, will almost certainly rule out embolism. Differentiation between cerebral hæmorrhage and thrombosis must be a matter of surmise. In favour of thrombosis are comparatively slow onset, perhaps some paralysis before the patient becomes unconscious, and the onset of the attack in the night when the circulation is low. Signs of muscular weakness or paralysis will be looked for, and a unilateral or crossed hemiplegia will help to localize the lesion. Changes in the reflexes will not have much diagnostic value unless they are unilateral, but this does not apply in brain or meningeal infections. In the examination of the pupils, again, we look for a unilateral irregularity to help in localization; pin-point pupils however are indicative of a pontine hæmorrhage. The importance of the ophthalmoscope has already been emphasized. A mydriatic may be required to give a satisfactory view of the fundus. Once more, a uni-

lateral finding, *viz.*, choked disk of one eye, will be of service in localizing the lesion.

Cerebral or meningeal infections generally give us the advantage of observation for some time before coma sets in, and only one further procedure need be mentioned, *viz.*, examination of the cerebrospinal fluid, which is applicable in all cases where the diagnosis is in doubt. No more should be removed than is actually required for diagnostic purposes. A good many general practitioners will have to be content with what can be learned from simple observation. The way the fluid runs into a test tube is not a guide as to the cerebrospinal fluid pressure. Only a manometer will tell us that. If we find blood in the fluid and it remains constant in every drop we may be fairly sure that it is not due to trauma from the needle. If there is any uncertainty the tube may be allowed to stand for awhile. Sedimentation of the red blood cells may leave a saffron or yellow coloured supernatant fluid, indicating that a hæmorrhage has

previously occurred in some part of the central nervous system where the blood could get into the cerebrospinal fluid. The colour may appear within two or three hours after the initial hæmorrhage, and may last two or three weeks. If red blood cells are not found in the coloured fluid one may be sure that the hæmorrhage has ceased. The cells disappear in two or three days. If evidence of hæmorrhage is not present any departure from the clear limpid appearance of the fluid points to a meningitis. It is scarcely necessary to say that if at all possible a cell count, globulin test, and bacteriological examination should be carried out, to say nothing of a Wassermann test, whether the blood Wassermann is positive or not.

Finally it should be remembered that there are diagnostic procedures which lie within the province of the neurological surgeon. Where there is doubt as to the existence of an operable intracranial hæmorrhage or a brain tumour his services should be obtained if at all possible.

COMMON DUCT STONE*

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THERE are several reasons for bringing this subject to the attention of the Surgical Section of the Academy. Doubtless most surgeons will agree with the statement that few conditions call for greater surgical judgment and technical skill, and any interchange of ideas directed to this point alone will be well worth while, but the main reason for presenting it is to point out once again the great difference in the mortality rate whenever cholelithiasis becomes complicated, and in addition to lay before you a few ideas in management which have developed out of the experience of some few years. R. P. Rowlands¹ makes the following statement: "It ought to be evident that the mere demonstration of gall stones in the gall bladder is not sufficient indication for operation. They are very common, and in many cases they cause no appreciable discomfort, or only such as can be readily relieved by medical treatment; but when symptoms of cholecystitis or of gall stones recur or

persist in spite of medical treatment, it is wise to recommend early operation in order to prevent a high mortality rate and other serious consequences of delay."

It was after reading this statement that I was led to make a study of my own cases of gall stones from the standpoint of complications, and from these findings to assess the risk to the patient from carrying around gall stones without complications. The analysis covers 102 cases, and as legitimate complications I have taken common duct stone, empyema of the gall bladder, and carcinoma of the gall bladder. The frequency with which stone is associated with acute pancreatitis makes the adding of this disease seem reasonable, but in this study it is not included.

CHOLELITHIASIS

	No.	Died	Percentage
Chronic	71	1	1.4
Acute	15	3	20.0
Common duct stones	11	1	9.1
Carcinoma	5	5	100.0

* Read before the Section of Surgery, December 19th, 1933, Academy of Medicine, Toronto.

A review of the literature reveals figures very similar. Thus, R. P. Rowlands² states that in 666 cases of cholelithiasis he found 20 per cent with common duct stones, and that in those cases in which he found common duct stones the death rate was 12 per cent. In 116 cases of cholecystostomy the death rate was 18 per cent, while in 436 cases where cholecystectomy was performed it was 1.6. Of course, cholecystostomy is used in bad risk cases and these figures are hardly fair to the operation. Judd and Marshall at the International Assembly of the Inter-State Post-Graduate Medical Association, in 1930, stated that the incidence of common duct stone was 13.2 per cent and that the mortality rate was 6.7. In cases of uncomplicated gall bladder stones in which cholecystectomy was performed the death rate was 1.66 per cent.

An analysis of this Table brings out some interesting features. In addition to showing the complication incidence of gall stones it is evident that when gall stones become complicated the mortality rate rises by the multiple of 6.5, or, to translate this into practical argument which the average patient can grasp, it means that at a conservative estimate it is from six to seven times more risky to carry uncomplicated stones than it is to have an early operation; it means that the patient with gall stones in the gall bladder has a 5 per cent chance of death from carcinoma; it means he has a 1 per cent chance of death from stone in the common duct, if that condition be complicated by jaundice and infection; and it also means he has a 3 per cent chance of death if acute symptoms go on to empyema of the gall bladder. Another point to which special attention should be paid is that carcinoma of the gall bladder is by no means uncommon and in this series it was always associated with stones. The mortality rate from this disease was 100 per cent.

Common duct stone, as I have said, is one of these complications, for we believe that practically all common duct stones are born in the gall bladder. While the common duct stones remain free in the duct and are uncomplicated they cause no more damage to the patient than if they remained in the gall bladder, nor is the risk of their removal noticeably greater. The advent of jaundice is a serious complication, and super-imposed infection in addition to the

jaundice is a formidable one. The incidence of common duct stone in gall-stone disease is above 10 per cent, and it may be stated that 2 per cent of these have a painless history, and that 27 per cent have a jaundice-free history. It appears then that 98 per cent of common duct stones are painful and 63 per cent have a history of jaundice. On analysis, this means that of all the patients coming to operation for gall-stone disease only one-quarter of 1 per cent will have a painless common duct stone, and of all the cases of gall-stone disease coming to operation only 3 per cent will have a stone in the common duct which has not at some time in the past given rise to jaundice. But let us pause here for a moment to remember that until recently the common duct has been opened only if there was jaundice present or a history of jaundice, and if we explore these common ducts which appear dilated, or in which there is a suspicion of stone, the 10 per cent incidence of common duct stone in gall-stone disease may grow considerably, and, of course, if this be true, the incidence of symptomless common duct stones will be greater than 3 per cent. Now this 3 per cent, or 3 per cent plus cannot be ignored, and we are forced to admit that the plan of opening the common duct only when jaundice is present or when there is a history of jaundice is too conservative, and that all dilated ducts should be explored to prove or disprove the presence of stone.

PRE-OPERATIVE TREATMENT

Unless a patient be jaundiced when admitted to hospital the pre-operative preparation need not be unduly prolonged. On the other hand, if the patient is jaundiced, in order to obtain a satisfactory result, careful attention must be given to pre-operative treatment. A space of two weeks may be allowed to elapse from the onset of jaundice before operation is attempted, because unless infection is present little liver damage will result. During this time the laboratory investigation should be made. If, however, infection in the common duct is evident one should not delay, but should institute drainage of the biliary tract. In operating in the presence of jaundice one should keep in mind two important post-operative complications, hæmorrhage and kidney and liver insufficiency. There are two essentials in pre-operative treatment, first, the

administration of a sufficient quantity of glucose to build up the liver reserve, and measures directed towards increasing the coaguability of the blood. It has been the custom in recent years to administer calcium chloride intravenously, but it must be remembered that a quart of milk per day will give a patient as much calcium as he can assimilate and is probably just as effective as calcium intravenously. The jaundiced patient should be transfused either the day before or immediately before operation, because there is nothing at our disposal as effective as direct blood transfusion in preventing hæmorrhage. It is always wise to repeat the transfusion in two or three days after operation if the jaundice is not readily clearing up. Kidney and liver insufficiency are best combated by the administration of glucose in normal saline.

THE OPERATION

The proper way to proceed after opening the abdomen and making sure that hæmostasis is absolute is first of all to examine the common duct. In fact, this should be a routine in all cases of gall-bladder surgery, with or without jaundice. First, visualize the region of the duct by seizing the gall bladder and drawing it up into the wound, pointing the fundus towards the right shoulder. Then raise the pouch of Hartman, and this brings into view the hepaticoduodenal ligaments, which, after these are divided, exposes the common duct. If the duct is not located in this way one should always make sure of its situation by tracing the cystic duct down to its junction with the common duct, and if one is still uncertain as to whether or not the structure in view is the common duct or portal vein, there need be no hesitation in using a fine aspirating needle, and if blood is withdrawn this is evidence that the portal vein has been tapped. No harm results from this and a further search must be instituted. After the duct has been exposed, or even before its exposure, it should be carefully palpated with the fingers of the left hand. With the index finger or the middle and index finger in the foramen of Winslow and the thumb on top, gently palpate the duct. It is wise not to squeeze the duct too firmly, for while a large fixed stone may be felt with any amount of pressure, yet a smaller or several small stones may slip away and escape detection. Indeed, there are many stones

which cannot be palpated, and in these cases the size of the duct must be taken into consideration in deciding whether or not it should be explored. When jaundice is present, or when there is a history of jaundice, the duct should be opened without debate. Until recently the duct was opened only where there was jaundice or a history of jaundice, but this plan is too conservative, and common ducts should be opened if dilated or if there is pancreatitis involving the head of the pancreas.

The duct is opened by a longitudinal incision close to the cystic duct, but before making the incision it is wise to steady the structure either by an Allis forcep, or, better, by passing a stay-suture on either side of the line of incision. After opening the duct exploration takes place. No matter what method is used for exploration, always avoid trauma. Ordinary stone seekers do very well in most cases, but irrigation with saline and a cannula is an excellent way. Recently we have used a urethral sound and sound for stones, either through the cystic duct or directly through the opening in the common duct, as is done through the urethra in the urinary bladder. By using traction on the cystic duct the valves of Heister are so flattened out that the sound passes readily.

There are two essentials in doing common-duct surgery. The first is sufficient exposure of the duct, which is facilitated by dividing the hepaticoduodenal ligament and thereby locating the junction of the cystic duct with the common duct, and, whether the incision be through the rectus muscle or a modified transverse incision along the costal margin, spinal anaesthesia is certainly a great help. Secondly, a good assistant is absolutely necessary for success.

After exposing the common duct and establishing its patency, the question arises as to whether or not the gall bladder should be removed or drained. It appears to me that the question of drainage and the type of drainage cannot be too carefully considered. In the first place, the function of drainage is twofold, to remove the infective matter and to act as a safety valve for the suture line in the common duct. If infection is present drainage is necessary, but the type of drain used will depend on whether or not the drainage is for a short time, as in a case of infection alone, or

for a prolonged period, as in the case of chronic pancreatitis. In the former instance a small tube directed upwards towards the liver is all that is necessary, while in the latter a T-tube would appear to be the proper thing, because as time goes by its use will enable one to control how much bile may be allowed to enter the intestinal tract or escape externally. If the common duct is free from infection there seems no very good reason why it should not be carefully closed, and a safety valve drain placed in the gall bladder or in the stump of the cystic duct, to relieve tension on the suture line.

If one remembers that gall stones are due to a combination of metabolic upset plus the concentrating action of the gall bladder, one comes to realize that any gall bladder which has once formed a stone or stones should sooner or later be removed because of the likelihood of its forming more. However, as a conservative rule, the gall bladder should not be removed in the presence of jaundice, but should be drained, because if one fails to get relief from chronic obstructive jaundice an existent gall bladder is very necessary for anastomosis into the stomach.

From the standpoint of surgery cases of common duct stone fall into certain well defined types: (1) stone in the duct without a history of jaundice; (2) stone in the common duct without jaundice, but with a history of intermittent jaundice; (3) stone in the common duct with jaundice, and complicated further by infection.

Cases without jaundice, but with a history of intermittent jaundice, and cases without a history of jaundice.—The procedure should be to open the duct, remove the stone or stones, close the duct, and remove the gall bladder, if diseased, and drain through the cystic duct, after the manner of Whipple; or do not drain at all and depend entirely on the secondary drain which is always placed in Morrison's pouch and in close proximity to the suture line in the common duct. In this case the drain is for safety-valve function.

Stone in the common duct with jaundice.—The rational treatment should be to open the duct, remove the stone or stones, close the duct with fine interrupted catgut sutures, re-inforce the suture line with a patch of omentum, and drain the gall bladder. The cases in which I

have used this plan have been highly satisfactory. It is understood that the gall bladder should be removed at a later operation, to ensure a permanent cure of the gall-stone disease, but as a primary operation the above is ideal—a minimum of trauma to the common duct and a safety-valve drain by way of the gall bladder.

Stone in the common duct with jaundice further complicated by infection.—In this case the procedure should be to open the duct, remove the stones, drain the duct for infection with a small drain directed towards the liver or a T-tube, and then drain the gall bladder. This procedure, as in the former case, is a primary operation to be followed later by removal of the gall bladder. When infection is present the swollen œdematous cystic duct is not sufficiently patent for immediate drainage, which is necessary for the infection.

Cases with associated pancreatitis.—The question of prolonged drainage comes up in this type of case, and the procedure to be followed here is to open the common duct, remove the stone or stones, and drain the duct with a T-tube. If the gall bladder is functioning drain it, but, if not, remove it. The T-tube is most useful in this type of case, because as time goes by a daily increasing amount of bile can be made to pass into the intestinal tract, and this has a very beneficial effect on the patient's sense of well being. Some feel that the T-tube is an ideal way to drain the common duct and use it for all cases, but, while it has been a very great advance in the management where prolonged drainage is necessary, yet I have not come to the point where I think it should be used in cases requiring drainage for a week or ten days only. The T-tube is allowed to remain in cases where prolonged drainage is necessary for a period of from 2 to 3 months, and at the end of that time is easily removed by gentle traction.

No matter what has been done to the common duct or gall bladder in the way of opening or draining them, just before the abdomen is closed a small split drain should be placed near the junction of the cystic and common ducts, with one limb going downward towards Morrison's pouch and the other limb running in close proximity to the opening in the common duct. This small drain takes care of any leaking which may occur. If leaking should occur it is important not to remove this drain until the sinus in the abdominal wall is well established, because

if it is removed before this has occurred the more solid structures in the abdominal wall will fall together and form a trap, causing the bile to accumulate in the subhepatic space, which sooner or later becomes infected and requires the institution of proper drainage to bring about closure.

CONCLUSIONS

1. That uncomplicated gall stones should be regarded more seriously and operation advised.
2. That carcinoma of the gall bladder is a preventable disease.

3. That not only must the common duct be opened in cases with jaundice or a history of jaundice, but also if there is dilatation of the duct or if there is induration at the head of the pancreas.

4. That in cases on uncomplicated common duct stone the duct need not be drained.

5. That the T-tube is ideal for prolonged drainage of the common duct.

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PROGRESSIVE EXOPHTHALMOS FOLLOWING THYROIDECTOMY*

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THE subject of progressive exophthalmos following thyroidectomy has received considerable attention, especially in the last three or four years. There are however, apparently less than 40 cases reported in the literature, but there must be many others not recorded. In the past year and a half 3 have come under my observation. These cases bring forcibly to our attention the fact that the cause of exophthalmos in Graves' disease is still unknown, and that medical measures of treatment, at least, are of little avail.

Naffziger,¹ of San Francisco, describes the condition as follows.

"After thyroidectomy is performed, clinical improvement follows, except that the exophthalmos does not disappear. In a variable period, often within three or four months, it becomes evident that the proptosis is increasing; an increased fullness of the lids is noted; then lacrimation and epiphora occur. A watery appearance of the scleral conjunctiva is followed first by oedema near the inner canthus and then by swelling, which spreads rapidly, with protrusion of the inferior palpebral mucosa. Diplopia and lack of parallelism of the eyes are followed by increased limitation of the movements of the globe, and downward movements are the only ones retained ultimately. During the increasing protrusion of the eye through these stages, the lids no longer completely cover the globe, and the cornea becomes exposed. Such patients are said to be suffering from malignant exophthalmos, the severe ones progressing to the stage of corneal ulceration and infection."

I desire to record the following cases.

CASE 1

Mrs. H., aged 51, developed in March, 1931, nervousness and palpitation, with elevation of blood pressure,

and later swelling of the feet. The basal metabolic rate in August, 1931, was plus 35 per cent. Operation was performed on August 19, 1931. The pathological diagnosis of the gland was—subinvolution stage of a previously hyperplastic thyroid.

The patient returned home on September 6, 1931, and states that she took 15 drops of Lugol's solution three times daily, for four months. Her eyes were lacrimating for a week after leaving hospital, and the day after return home she had swelling of the lids. Her heart was rapid from September to Christmas, 1931. In the fall of September, 1931, she developed terrible headaches and vomiting, her vision began to fail, and at times she had double vision. By April, 1932, she was much worse in general, the eyelids puffed again, vision was worse, and lacrimation and burning sensation of the eyes were more and more marked. She had a basal metabolic rate taken in April, 1932, which was minus 11 per cent. Thyroid was taken (amount unknown), for ten weeks. She felt she was much more nervous and worse in every way after this.

When I saw her for the first time at her home in May, 1932, she presented the eye-picture noted by Naffziger—oedema of lids and face, oedema and redness and protrusion of the conjunctiva, lacrimation and photophobia. There was moderate exophthalmos, with increased intraocular tension, especially of the left eye. She had apparently had a pneumonia, with a few signs still persisting. Her blood pressure was 158/90; pulse 100. The blood pressure in the next few months varied from 116/66 to 172/100; the pulse was also variable. She has shown much evidence of instability of the nervous system, with many hysterical symptoms, and at times angioneurotic oedema and paroxysmal tachycardia. She had an apparent pyelo-nephritis and sinus infection last Spring, after which her eyes became worse. She showed a secondary anaemia, which responded to iron and diet. The blood Kahn, urine, spinal fluid, and skin tests were all negative. Her nervous symptoms were better after taking ergotamine. I was unable to obtain a basal metabolic rate until the patient was taken to hospital in May, 1933, when it was found to be minus 18 per cent. X-ray of the sella was negative. Blood calcium was 10.4; blood cholesterol, 381. She was placed on thyroid, grs. 5 (B. & W.), twice daily, and Lugol's solution, and also physostigmine salicylate, gr. 1/30, three times daily. There has been considerable improvement since, dating really from the time ergotamine tartrate was given.

* Read before the North Pacific Society of Internal Medicine, Vancouver, B.C., on October 13, 1933.

CASE 2

The second case was a man, aged 63, seen in May, 1933, complaining of soreness, protrusion and watering of the eyes of four months' duration. He had been admitted first in November, 1931, with symptoms of exophthalmic goitre, of one and a half years' duration, with exophthalmos for nine months. He had had iodine and bed rest for one month in April, 1931. In November, 1931, his basal metabolic rate was plus 38 per cent, and plus 24 per cent. He showed marked exophthalmos, tremor, etc. He was given Lugol's solution for thirteen days, and thyroidectomy was performed. The pathological diagnosis was—subinvolution stage of a previously hyperplastic thyroid. He was discharged after four weeks in hospital. He put on weight and improved in general, but he noted no change in the exophthalmos. One year after operation the eyes became progressively worse, with marked proptosis, oedema, lacrimation, etc.

He was admitted again to hospital on May 2, 1933. His basal metabolic rate was minus 23 per cent prior to admission in April, 1932; on May 5, 1933—minus 2; May 8th—minus 5; May 17th—minus 11. His blood pressure was checked night and morning daily and varied from 232/140 to 142/85. The morning blood pressure averaged 20/5 lower than the evening. The blood Kahn test was negative; urine, negative; blood calcium, 9.8 mg.; blood cholesterol, 245 mg. An x-ray of the sella turcica was normal. Tonsils, septic; thyroid, not enlarged; no local recurrence.

Eye examination: "Marked exophthalmos, both eyes, equal. Marked folding of the palpebral conjunctiva over the lower half of the sclera is thrown into a transverse fold at the lower limbus. Tension normal and equal. Pupillary reaction, normal. Limitation of lateral movements of eyes."

In hospital he was given small doses of thyroid and Lugol's solution, ergotamine tartrate, and a low fat diet. He was discharged on June 5, 1933, and instructed to take Lugol's solution, thyroid grs. 5 (B. & W.), once daily, and physostigmine salicylate, and to report to the outdoor clinic. He failed to report, and stopped taking any medication, as he saw no improvement. He was looked up, and examined again on August 4, 1933, when the eye condition, especially that of the right eye, was much worse. He was again put on thyroid and Lugol's solution. The severe oedema of the conjunctiva of the right eye became worse, and he was sent into hospital and had an excision of a portion of the conjunctival sac and a tarsorrhaphy done on August 21, 1933, by Dr. L. H. Leeson. He was discharged from hospital on September 14th, on Lugol's solution and thyroid, and also on pituitary substance, grs. 5, three times daily. The basal metabolic rate, taken on August 15th, had been minus 3 per cent. He has had less discomfort since the eye-operation.

CASE 3

A man, aged 63, seen on August 30, 1933, had been operated on for exophthalmic goitre in September, 1925. He had, prior to his operation, a history of fourteen months' duration, with loss of weight, nervousness, dyspnoea, and bulging of the eyes. His basal metabolic rate was plus 4 per cent on September 10, 1925, and plus 6 per cent on September 11, 1925. The blood pressure then was 124/84; pulse 84. Thyroid, "not markedly enlarged". Pathological report: "mildly toxic thyroid".

This man stated that there was much improvement after the operation in September, 1925, and that the protrusion of his eyes decreased by one-half, but became worse again about two years after operation, and had been especially bad for seven or eight months past. Vision had failed, and the eyes, especially the left, had become more prominent, more and more watery and red, and the lids puffy; double-vision had been noted in the past seven months. He had had, apparently, no Lugol's solution before operation. He states he took 9 drops three times daily for about two months following the operation, and none since. No thyroid medica-

tion was taken at any time. His basal metabolic rate in 1928 was plus 4 per cent, and about two years later minus 12. He felt tired and sleepy and less energetic.

Examination showed: signs of exophthalmos, with chemosis of the conjunctiva, and some haziness of the media. Mouth; septic teeth. Tonsils, small. Thyroid, plus 1, diffuse both lobes; no thrill or bruit. Heart, 1 inch to left; slight impurity of the 1st sound at the apex. Abdomen, negative. Deep reflexes, active. Tremor of hands, ii. Extensor test, normal, one minute. Blood pressure, 155/85. Pulse, 72. Blood Kahn test, negative. Blood count, normal. Urine, normal. Cholesterol, 150 mg. X-ray of the sella, negative. Basal metabolic rate, plus 8.

This patient was put on Lugol's solution, mm. 10, three times daily, and physostigmine salicylate, gr. 1/30, three times daily. On October 12th, his basal metabolic rate was minus 10.

Here then we have three patients—all with a severe disabling condition, even though the supposed cause of that condition had been removed. We note that all three have some foci of infection, that all three still have unstable nervous systems, that two had been given iodine for two weeks prior to operation (Cases 1 and 2; Case 3 had none). One took iodine post-operatively for four months. Patient 1 took iodine for three months, 5 drops a day; and patient 2, for two weeks only. Patients 1 and 2 have no evidence of local recurrence of the goitre. Two patients had definitely low metabolic rates; the third had a normal rate when seen. Two had slight or moderate, and one, marked, exophthalmos, prior to operation.*

Now, what is known about the production of exophthalmos in Graves' disease? The theories are many: overstimulation of the sympathetic; increased intraorbital fat, and oedema of the fat; retrobulbar venous engorgement; lymphatic stasis; injuries of the restiform body; pituitary changes, etc. Gleason has reported an idiopathic myositis, with all the ocular muscles eight times the normal size. Naffziger and Jones² reported on 6 patients with hyperplastic goitre, in whom the exophthalmos progressed after thyroidectomy. The metabolic rates varied from normal to minus 32. Vision was impaired seriously in 5, with swelling of the optic discs. During the operations performed for the eye condition (intracranial removal of the orbital plate) specimens of the eye muscles were removed and found to be three to eight times their normal size, showing changes from oedema to hyalinization, and fibrosis. Semmes³ reports that in operating on one of these cases of progressive exophthalmos showing a basic metabolic rate of minus 15

*Since the above paper was written all these patients have improved considerably on varying amounts of thyroid substance and Lugol's solution.

and a cholesterol of 390, he found the eye muscles cedematous and ten times normal size, but found that there was almost no orbital fat present.

H. Stewens⁴ reported a case in a man of 52, in whom an x-ray showed a strikingly small sella turcica. No mention is made of the metabolic rate. Thyroid medication was tried, but the chemosis and edema became worse. The Abderhalden reaction showed increased catabolism of the hypophysis. He was treated with hypophysin and pituitrin for several months. The exophthalmos and orbital edema gradually subsided. Zimmerman⁵ published reports of 8 cases where the metabolic rate had been brought to normal or below by thyroidectomy, and the exophthalmos had not been accompanied by other manifestations of hyperthyroidism. The intervals between operation and the time of increased prominence of the eyes ranged from three to twelve months. The ages were from 19 to 53 years. He states that it is significant that none had received iodine before the onset of the eye changes, except in the pre-operative period and during the first few days after operation. Once the eye condition had developed, it was neither improved nor made worse by thyroid medication, and no great improvement occurred with the use of Lugol's solution. Earnest and Sager⁶ report a case of unilateral exophthalmos following thyroidectomy. The basal metabolic rate was plus 33 prior to operation, and zero one year later. Gasteiger⁷ reports one case, and expresses the opinion that the eye manifestations were myxedema symptoms. Others reporting cases have been Burch,⁸ Roeder, and Killins.⁹ It must be mentioned that Crile has apparently produced results in hyperthyroidism by suprarenal sympathectomy; and Arn, of Dayton, Ohio, (in discussion of H. M. Clute's paper¹⁰), reported relief of severe exophthalmos and other symptoms of persistent hyperthyroidism in three cases, after bilateral suprarenal denervation.

As far as the local changes go in the production of this condition, then, it appears that the increase in the size of the eye muscles and intraocular edema is a definite finding, but what initiates this apparently irreversible change? Benedict¹¹ states that the exophthalmos is not dependent on the toxicity. He mentions 6 cases with malignant exophthalmos,

with the loss of one or both eyes. The basal metabolic rate was essentially normal, and no drugs helped the condition. Crile¹² makes the statement that severe post-operative exophthalmos is usually due to hypothyroidism, and that care must be taken not to perform a second operation on the cases because of a suspected hyperthyroidism. Resection of the thyroid gland evidently breaks the chief link in the unknown chain of factors concerned in Graves' disease, and in most patients the exophthalmos recedes (7 out of 10, according to Clute), and the patients remain well.

What goes wrong in these progressive cases? Why does the exophthalmos increase, not only in the real recurrences of hyperthyroidism but also as in those cases reported, where there is often a hypothyroidism? Is it a dysthyroidism alone, as believed by Plummer, with a deficiency of the normal? Boothby says that it is theoretically possible to have a combined normal and abnormal thyroid secretion so small in amount that when the latter is suppressed with iodine the patient becomes definitely myxedematous, and when iodine is not administered there is a combination of the symptoms of myxedema with those of exophthalmic goitre. Rowe and Lawrence¹³ speak of transition states in thyroid cases from hyper- to hypo-thyroid, in which all of the characteristics of the first state do not recede with the same velocity, and we thus have mixed signs and symptoms of under- and over-activity of the thyroid in the same patient at the same time.

H. S. Plummer¹⁴ remarks that he has never quite given up the concept that a third agent exists, which produces the ocular changes. He reports a case that before operation had a metabolic rate of plus 80, and after operation, minus 14, nervous phenomena, and progressive exophthalmos; and when placed on iodine, the nervous phenomena would disappear, the exophthalmos recede, the basal metabolic rate drop to minus 28, and edema, slow speech and characteristic myxedema appear within two weeks. When iodine was given and the metabolism maintained at the normal level with thyroxin there was no evidence of the disease except slight exophthalmos. He believes that in Graves' disease there are probably three agents concerned: one which increases metabolism (thyroxin); one which produces nervous system changes (contained in desiccated thy-

roid); one which produces exophthalmos. Kunde¹⁵ found experimentally that all symptoms of Graves' disease could be produced by feeding thyroid or injecting thyroxin in the rabbit, (without the aid of any secondary product). In the normal rabbit excessive doses of thyroid produced only mild exophthalmos, but rabbits made myxœdematous by early thyroidectomy developed very marked proptosis. However, excessive thyroid feeding has never produced exophthalmos in man.

It is said that myxœdema never follows subtotal thyroidectomy unless there is also a thyroiditis present. If this is true it would suggest that infection may play a rôle in these cases of apparent paradoxical exophthalmos.

When we consider, then, that exophthalmos may occur and progress in three different conditions, (1) in definite exophthalmic goitre with increased basal metabolic rate, (2) in post-operative cases of this disease with decreased basal metabolic rate, and (3) in post-operative cases of Graves' disease with normal basal metabolic rate, we feel that the same factor must be present in all. The part of the thyroid substance which increases metabolism cannot be the agent. A thyroid substance deficient in iodine could perhaps be accountable, but then iodine medication has no very evident effect in curing or even preventing the condition. There appear to be irreversible changes in the eye muscles and orbit produced by some toxic substance. Is it due to infection, or to Plummer's third thyroid agent—or something else? What is the factor X? If Dr. Kunde can produce exophthalmos in animal with excessive feeding of thyroid, this would seem to belittle such a supposition. However, if an X substance is present in all three types it could be present in the myxœdematous animals, and thyroid feeding could cure the myxœdema but still be lacking in something (found in the living gland) to counteract the X substance. This is possibly produced also by overstimula-

tion of the sympathetic, for it is known that overstimulation of sympathetic fibres gives rise to the so-called sympathetico-mimetic substances—toxic amines. Some day it may be possible, then, to reduce to some common biochemical denominator (such as tyramin), the equation of clinical and experimental exophthalmos.

CONCLUSION

Progressive exophthalmos following thyroidectomy appears to be an enigma. We may call these cases what we will—paradoxical exophthalmos; combinations of hypo- and hyperthyroidism, due to persistence of an abnormal secretion, only partly cured by surgery. We may feel that infections play a part, that other endocrine products are concerned, that emotional and nervous strains and fear contribute, but the fact remains that this is a problem the solution of which involves the whole question of goitre.

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FIXATION ABSCESS IN ASTHMA.—P. A. Simon reports 14 cases of asthma in patients aged from 24 to 32, in which rapid relief was obtained by treatment with a fixation abscess. The success of the method appeared to be due to: (a) the powerful effect exerted by the derivative and decongestive action on the more or less latent bronchial inflammation; (b) a considerable discharge of microbial toxin; (c) a temporary production of fever accompanied by an intense increase in leuco-

poiesis, which permanently modified the resistance to the toxic-infection and restored the disequilibrium of the neuro-vegetative system; and (d) a psychotherapeutic action on persons of a neuropathic constitution. The contraindications for fixation abscess are anasarca, pulmonary tuberculosis, and diabetes on the one hand; and on the other hand, mild attacks which are not worth treating by a method which, though free from risk, is decidedly painful and immobilizes the patient for a considerable time.—*Thèse de Paris*, 1934, No. 355.

BRONCHOSCOPY IN THE DIAGNOSIS OF PULMONARY DISEASE

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IN presenting a paper on a certain phase of the diagnosis of pulmonary disease to a group of general medical practitioners it would seem unnecessary to direct attention to the importance of securing a careful history, and of making a complete physical examination and such additional studies as might be required to bring a case to a final conclusion.

In considering only the bronchoscopic aspects I wish to emphasize that all of the cases cited were carefully studied, and bronchoscopy was recommended only after the usual diagnostic measures were found inadequate. This conforms to the routine procedures carried out at the Bronchoscopic Clinic when a patient is admitted for diagnostic study, namely, history, physical examination, serological studies, roentgen examination and such bacteriological investigations as may be indicated.

While it may be necessary to treat certain patients symptomatically until a diagnosis can be arrived at one should never be content with this. A diagnosis of chronic cough, winter bronchitis, hæmoptysis, bronchial obstruction, is a mere makeshift and, while it may satisfy patients, is nevertheless inadequate to allow one to give a prognosis and prescribe proper treatment. A good history will often give a clue to the diagnosis. This, supplemented by careful examinations of the chest and sputum studies, will complete the diagnosis in many cases. In a certain group it is necessary to carry out roentgen studies of the chest to aid in arriving at a positive conclusion. Certain obscure cases must be further investigated before arriving at an etiological diagnosis. As examples of this may be cited a case of bronchial obstruction in which the lesion has been localized to a definite bronchial branch but the nature of the obstruction cannot be ascertained, or a case of suppuration which has been found to involve a certain part of the lung but which may or may not be a bronchiectasis or suppurative bronchitis. Additional

cases of "wheeze", obscure hæmoptysis, unexplained cough or other symptoms might be cited. It is in cases of this type that recourse must be had to bronchoscopy.

Bronchoscopy, a method of direct examination, is a rational and a commonly accepted procedure in medicine. It is performed without general anaesthesia, with a minimum of discomfort to the patient, and, in trained hands, it should be without mortality. Its use as a diagnostic aid has become so important that practically every large hospital has a bronchoscopic clinic.

The indications for diagnostic bronchoscopy must be discussed in a general way, as one might discuss the indications for a roentgenological examination of the chest. It is of value in all of those cases that cannot be unravelled by the methods commonly employed in the diagnosis of chest diseases. In every chest clinic there are undiagnosed cases; in every sanatorium there are a number of patients in whom tuberculosis is suspected but cannot be proved. It is important not only to rule out tuberculosis but to establish a correct diagnosis. Many of these prove to be cases of bronchiectasis; others are bronchial carcinoma. Unless these and other conditions are recognized early little can be accomplished by treatment. Certain anatomical diagnoses can often be made with regard to the portion of lung involved. Notable among these are bronchial obstruction and pulmonary suppuration.

Bronchial obstruction may be diagnosed clinically or by physical examination, and should always be recognized roentgenologically, especially if the patient is observed fluoroscopically or if films are made at the end of inspiration and expiration. The treatment depends entirely on the nature of the obstruction. If it is produced by an aspirated or endogenous foreign body bronchoscopic is the only treatment worthy of consideration. If the obstruction is caused by a growth it is necessary to

ascertain if this is benign or malignant. If benign, the growth may be removed by the help of bronchoscopy and further removals carried out if necessary. If the growth is malignant its character and degree of malignancy can be determined on the basis of histological study of bronchoscopically removed tissue. If there is a stricture of the bronchus bronchoscopic dilatation may be carried out. If the obstruction is produced by an extra-bronchial lesion causing compression stenosis bronchoscopy is definitely indicated, to ascertain the character of the process and to determine what plan of treatment is indicated. Delay in bringing a case of bronchial obstruction to a final conclusion may not only deprive the patient of his only chance to recover but will usually always lead to suppurative changes distal to the obstruction. If bronchial obstruction is long-continued, and in the presence of certain bacteria, bronchiectasis will develop.

Carcinoma of the bronchus.—One of the outstanding contributions of bronchoscopy in diagnosis is recorded in the literature of neoplasms of the bronchus. Prior to the advent of bronchoscopy the diagnosis of cancer was made by the pathologist, based on his findings at autopsy. A diagnosis during life was rarely made, and, when made, it was usually too late to start any form of treatment. The performance of bronchoscopy in cases of obstruction of a bronchus, persistent cough, unexplained wheeze or hæmoptysis has permitted of a positive diagnosis in many instances. In some of these the diagnosis of carcinoma was made sufficiently early so that surgical extirpation could be practised; in others radiation therapy was instituted. Among the earliest symptoms of bronchogenic carcinoma are cough and wheeze. A cough which remains unexplained for more than 3 or 4 weeks should be further investigated, and bronchoscopy should be added to the diagnostic measures if necessary. We are so prone to associate asthma with wheezing respiration. A wheeze is produced by narrowing of a bronchus. Since carcinoma more commonly involves the larger bronchi, direct examination of these bronchi would be the logical procedure if there was a question of stenosis.

Tuberculosis.—It has been commonly believed, even by many bronchoscopists, that bronchoscopy is absolutely contraindicated in tuberculosis.

Contraindications to bronchoscopy have much in common with contraindications to surgery in that no one would advise surgery in a tuberculous patient unless it was definitely indicated. It is not necessary to resort to bronchoscopy for diagnosis in the average case of pulmonary tuberculosis. There is, however, a large group of patients in whom tuberculosis may be suspected but in whom a positive diagnosis cannot be made. In these bronchoscopy is very clearly indicated. Bronchoscopy is also of value in explaining certain signs or symptoms that have developed in a known case of tuberculosis. It may be of value in establishing the cause of atelectasis. It has a very definite place in the study of children in whom lymph-node enlargement is producing bronchial stenosis or in whom a positive diagnosis cannot be made.

Pulmonary abscess.—There is usually no question of diagnosis in the average case of pulmonary abscess, particularly if there is a history of operation or acute pulmonary infection with the development of the usual symptoms, physical signs, characteristic sputum, and roentgenological evidence of a localized inflammatory area with abscess and fluid level. Pulmonary abscess may, however, develop secondarily to foreign body obstruction or bronchial carcinoma. If there is a question in these cases bronchoscopy is indicated as a diagnostic procedure. It is generally recognized that bronchoscopy has a very definite place in the treatment of pulmonary abscess.

Bronchiectasis.—The classical case of advanced bronchiectasis should present no diagnostic difficulties. One can often make a provisional diagnosis after inspecting a twenty-four hour specimen of sputum. It may be stated in passing that the diagnosis in these advanced cases is of remarkably little value and contributes nothing to our knowledge of the treatment. If one wishes to accomplish anything by treatment one must recognize these cases in their incipency. In the usual case when the changes are minimal a diagnosis is often attended with difficulty and in many instances it is largely inferential. These are the cases that often are listed as chronic cough, chronic bronchitis, or suspected tuberculosis. A positive diagnosis can be made only by roentgenological examination of the chest following the instillation of some form of radiopaque substance into the tracheo-bronchial tree. This statement is based on the

observations made by checking the findings of many clinicians who have referred patients to the bronchoscopic clinic either to corroborate the diagnosis of bronchiectasis or in whom it was believed that bronchiectasis was not present. It has been repeatedly observed that many patients with nasal-sinus infection present respiratory symptoms that cannot be distinguished from those observed in cases of early bronchiectasis. In not a few instances these cases have been diagnosed as suspected pulmonary tuberculosis and are lodged in sanatoriums for many months. Cases of nasal sinus suppuration with bronchial symptoms commonly have a suppurative bronchitis; if allowed to continue this often will develop into bronchiectasis. One can distinguish between these cases only by the use of pneumonographic aids. Lesions involving the lower lobe of the left lung behind the heart shadow also are commonly overlooked in the routine examination. In these pneumonography is im-

portant. While radiopaque substances may be introduced into the tracheobronchial tree by one of many methods there is a distinct advantage in bronchoscopic pneumonography. This method permits of accurate placement of the material to be instilled after pus has been aspirated from the bronchi; it also gives additional knowledge that can be secured only by direct inspection of the air passages.

These few clinical and anatomical entities give one an insight into the possibilities of bronchoscopy as a diagnostic aid. Its importance lies in the fact that it is a method of direct examination; information secured by direct methods is of a positive character. Bronchoscopy in trained hands is a safe procedure and should be performed without general anaesthesia. Its field of usefulness should be practically unlimited in the realm of chest diagnosis; it is indicated in all obscure chest cases that cannot be diagnosed by the ordinary methods.

CARCINOMA OF THE JEJUNUM

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EPITHELIAL tumours of the small bowel are interesting because of their infrequency. This is in contrast to the same type of growth in the large bowel, which is relatively common. The pathological condition is not the only interest in these cases. Clinically, they present a problem for diagnosis, and a correct diagnosis is not always made preoperatively, in spite of the most careful study.

On March 25, 1933, I saw the following interesting case in consultation with Dr. Guy Hanley, of Toronto.

Mr. J., aged 70, married, retired, was seized with upper abdominal pain, colicky in nature, about 10 a.m. He was helping his son in a butcher shop and continued at work until 5 p.m., when he was forced to go home. We saw him the same day about 7 p.m. He was having severe colicky pain associated with vomiting. The vomitus at first was bile-stained and later clear fluid. He stated that this was the first attack of abdominal pain he had had, and persisted that there had been no change in his general health. There had been no loss of weight and no change in bowel habits.

Physical examination.—The patient was a well developed, fairly well nourished adult. The skin and mucous membranes were normal. The heart and lungs were negative; blood pressure 140/100. The abdomen was scaphoid; no visible peristalsis; no masses palpable. There was slight tenderness but very little involuntary

rigidity. Fluid splash was obtained in the right lower quadrant. Rectal examination was negative; slight prostatic enlargement was detected, but no nodules.

The patient was given morphia, gr. $\frac{1}{4}$, with atropin, gr. 1/150, hypodermically and sent to Toronto General Hospital. He vomited after receiving the injection and got complete relief from pain. He was quite comfortable during his stay in hospital. There was no recurrence of pain. Repeated examination of the abdomen did not reveal the cause of his trouble. Temperature, 98°; pulse, 78. The white blood cell count was 7,800. Non-protein nitrogen, 28. The urine contained a few pus cells. A barium enema was given, but was negative. A gastric series was done, with negative results, except that there was evidence of adhesions at the terminal ileum, and it was suggested that he might have had an atypical attack of appendicitis.

The patient was quite comfortable, and, although we had not made a diagnosis, we felt that it would be safe to allow him to go home, with instructions that he report any recurrence of his pain. He was discharged from hospital on March 27th and returned to his home. He had a recurrence of pain the following day, but the attack was of short duration. He went to his summer home in northern Ontario, early in the summer. He had discomfort part of the summer. This pain would come on about four hours after eating, and occasionally he would vomit, and, when he did, he noticed that he was relieved. On August 31st he had a severe attack of pain, colicky in nature, with frequent vomiting. He returned to the hospital, when we investigated him again. We repeated the previous examinations with similar result, except that the radiologist reported that there was evidence of distension of the small bowel. Physical examination of abdomen at the time showed very slight distension, if any. There was some tenderness, without

involuntary rigidity, in the right iliac region. While this was his second admission to the hospital, and we felt we had investigated him carefully, we were still unable to arrive at a definite diagnosis. We thought, however, that he had some adhesions at the terminal ileum, which were producing a kink of the small bowel at this region. We decided that, even with the negative physical findings, we were justified in recommending exploration of his abdomen.

Operation.—Spinal anaesthesia was employed. The abdomen was opened through a low, right rectus incision. A definite Lane's kink was found and divided. This did not appear to be sufficient to account for his symptoms, so the abdomen was explored. A hard growth was found in the jejunum. This was encircling the bowel and producing partial obstruction. The proximal bowel was distended and thickened, and numerous neighbouring mesenteric glands were enlarged. A resection was performed, 14 inches of jejunum being removed, with a wedge-shaped piece of mesentery which contained the enlarged glands. An end-to-end anastomosis was done, sewing a small rubber tube into the lumen of the bowel at the point of anastomosis. This prevents obstruction from edema, which may occur a few days after the operation. The abdomen was closed in layers, without drainage.

The *pathological report* (by Dr. W. L. Robinson) was as follows, "Adeno-carcinoma; secondary in the regional lymph glands. This is a loop of small bowel which measures 35 cm. in length. In the central portion of it is an annular hard carcinomatous growth which is greyish white in colour, completely encircling the bowel and producing a stenosis. The regional lymph glands draining this portion are enlarged and quite firm in consistency. On section they are greyish white in colour, with yellowish opaque areas scattered through them. Microscopically, a section of the growth in the bowel shows it to be made up of masses of atypical epithelial cells forming pseudo-glands. This growth is confined chiefly to the mucosa, with some extension into the underlying muscle tissues. Sections of the lymph gland show it to be invaded by a growth similar to the primary.

The patient's convalescence was uneventful. He returned to his home on September 23rd, seventeen days after the operation.

Carcinoma of the small bowel is rather rare and is estimated as constituting between 2 and 3 per cent of all intestinal carcinomas. Craig¹ reported a series of 4,684 cases of carcinoma of the gastrointestinal tract; in this group there were 36 cases of primary carcinoma of the small bowel. Bunting,² in 2,200 post-mortem examinations at Johns Hopkins Hospital found 104 cases of gastrointestinal carcinoma: 3 in the duodenum and 1 in the ileum.

There are two types of carcinoma of the small bowel: (1) carcinoid tumours; (2) adenocarcinoma. The former are not very malignant. They metastasize very late, if at all, and have been termed the rodent ulcers of the intestine. Adenocarcinoma is, however, the commonest type and sometimes arises from a pre-existing polyp. These tumours are quite malignant and metastasize early. Neighbouring glands are involved first, and, later, the liver, lungs and peritoneum. Over 50 per cent of these cases operated on at the Mayo Clinic had glandular

involvement. In Craig's series over 80 per cent were males, and he found the prognosis most favourable when the tumour was located in the jejunum, and most unfavourable when the ileum was involved.

DIAGNOSIS

The symptoms of carcinoma of the small bowel are difficult to analyze and an accurate diagnosis is almost impossible. This is particularly true in the early stages of the disease, before the onset of obstruction. The most constant symptoms are colicky pain, vomiting, and rapid loss of weight. Johnston³ finds hyperperistalsis the most constant, and observed 3 cases in which visible peristalsis at the time of examination could be detected. X-ray examination is of questionable value. A patient, with the above symptoms, when no pathological cause can be found to account for them, should have the advantage of exploratory laparotomy.

TREATMENT

Resection, wide of the growth, should be performed. This should provide removal of all involved lymph glands, if possible. The resection should include considerable normal bowel on each side of the growth with a wedge-shaped piece of mesentery. The continuity of the bowel should be restored by end-to-end anastomosis. A small rubber tube sutured into the lumen of the bowel at the line of anastomosis provides a good safety valve and prevents the blocking of gas in case of local edema.

In the after-treatment of these cases it is worth while passing a duodenal tube and leaving it down for two or three days. The nurse should aspirate it every four hours. This is particularly applicable when the growth is high in the small bowel, and has a twofold function, adding to the patient's comfort and taking tension off the suture line at the point of anastomosis.

PROGNOSIS

The post-operative longevity in these cases is fair, according to Craig's study of cases at the Mayo Clinic, patients living from two months to eight years after operation. The difficulty of early diagnosis is the stumbling block. The symptoms are essentially obstructive, and stenosis is likely to be advanced before any surgical treatment is instituted. This time

factor, rather than any unusual malignancy, explains the high frequency of lymphatic involvement and the fact that, when diagnosed, a large number of cases are inoperable.

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RELIABLE SPINAL BLOCK ANALGESIA

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THE characteristic advantages of spinal block analgesia over other forms of anæsthesia are now almost universally recognized. Notably, the complete muscle relaxation, the constriction of the small bowel, the rapid return of normal body functions, and the low incidence of operative shock and of post-anæsthetic complications are generally appreciated. Nevertheless, spinal anæsthesia has, in many centres, met with more or less complete rejection by surgeons or anæsthetists, or by both. This is an unfortunate state of affairs, because spinal block can, and should, form an important component of the anæsthetist's armamentarium — one, if not abused, of very real value.

After experiencing in our service more than 1,600 carefully observed and recorded administrations of spinal analgesia, over a five-year period, the writer is prompted to make the following observations.

OBJECTIONS

The outstanding reasons for spinal anæsthesia being frowned upon appear to be two in number:—

1. Severe collapse (even death, rarely) sometimes followed the spinal injection. The writer would interpret this phenomenon in one, or both, of two ways. First, the anæsthetic agent reached the fourth ventricle in a fairly high concentration, producing a paralysis of one or more of the vital centres (challenged by certain investigators who have experimented with normal animals, but possibly a real factor in human beings, especially if in a debilitated condition). This would suggest faulty technique. The second interpretation would be that the patient did not well tolerate the appreciable alterations of blood pressure caused by a certain

amount of pooling of blood in the splanchnic region, resulting in temporary brain anæmia, with or without anoxæmia. This would indicate that spinal anæsthesia had been employed ill-advisedly in an unsuitable subject. This latter misadventure can, with ease and surprising accuracy and confidence, be avoided by a proper categorization of the patient pre-operatively as to surgical risk. Our convenient and satisfactory method of such categorization has been previously described by the writer elsewhere.¹

In case any degree of collapse should appear (it rarely will if the rules for spinal anæsthesia are strictly adhered to) the anæsthetist must have ready at hand the following emergency devices: oxygen,—for anoxæmia; carbon dioxide, as an occasional whip in respiratory embarrassment; stimulants, notably coramine, for circulatory distress; intravenous salines, preferably with glucose, to build up blood volume.

2. Inconsistency of the anæsthesia is the other chief accusation raised against spinal block. Nothing will turn the surgeon more irrevocably against "spinals" than never to be certain how long his anæsthesia is going to last, or how wide a field it is going to cover. Conversely, the surgeon's confidence is readily established if he can be absolutely sure of having a definite anæsthetic field for a certain minimum period of minutes with all the advantages that spinal analgesia offers.

RULES AND ROUTINE

In view of the foregoing conceptions, and because spinal anæsthesia enjoys a good reputation among both surgeons and patients in our hospital, the routine of our Anæsthetic Department is here described.

Indications and contraindications. — Spinal analgesia is applicable in grade 1-risk patients for all surgical procedures below the diaphragm, and also in grade 2-risk patients, with reservations. The better the patient's general condition, the more suitable he is for spinal anaesthesia. Spinal block analgesia has two particularly valuable applications, *viz.*, in diabetic patients, and in big powerful, athletic males who are difficult to induce, and still more difficult to get safely relaxed, with general anaesthesia.

Spinal block (with the exception of the purely "saddle-area" stovaine procedure described later) is not at all suitable for grade 3- or grade 4-risk patients (poor and very bad risks). The outstanding definite contraindications are anaemia, collapse, cardiac deficiency, low blood volume, essential hypertension, general debility, advanced senility, and the existence of a spinal cord lesion. Further, any patient who as a result of the preliminary medication here set out reaches the operating room with a failing pulse, or with a systolic blood pressure as low as 90 mm. Hg, or with a dusky or cyanotic colour is definitely *not* suitable for spinal block. Spinal analgesia has been disappointing in our series in three cases of obstructive jaundice (precipitation of the novocaine by bile salts in the cerebrospinal fluid?). And, finally, spinal anaesthesia should not be employed unless a gas-oxygen machine is readily available—to furnish oxygen if any degree of anoxaemia should develop, or to induce sleep if the patient should become restless, apprehensive, or nauseated.

PRELIMINARY MEDICATION

It is very desirable that patients for spinal analgesia should have very little realization of their surroundings and yet should be able to cooperate slightly to facilitate the lumbar puncture. Accordingly, the following premedication is given as a routine to adults: one hour before operation, nembutal* gr. iii, with half a glassful of water; pantopon (Roche), gr. 1/3, and hyoscine, gr. 1/200, hypodermically;

* It would appear at this stage of our experience that oral sodium (sodium hexyl-ethyl-barbiturate) is preferable to nembutal in patients past middle life, in that we observe less restlessness and delirium, but the incidence of nausea on the operating table, especially with younger patients, seems higher than when nembutal is used.

one-half hour before operation, pantopon, gr. 1/6, hypodermically, if the patient is still alert or apprehensive. Once the initial premedication is given, the patient must be strictly undisturbed, and sleep should in every way be encouraged.

THE TECHNIQUE FOR NOVOCAINE SPINAL BLOCK

Place the patient on a table which can be tilted into the Trendelenburg position, lying on his side, (preferably the right side for a right-handed anaesthetist), with the knees and head drawn as closely together as possible. Have the patient held securely in this position by an attendant. The anaesthetist, in sterile gloves, should prepare a wide area on the patient's back with iodine, and surround the proposed area of injection with sterile towels. The "low" injection is made between the third and fourth, and the "high abdominal" between the first and second lumbar vertebrae.

A generous-sized skin wheal is raised at the desired point, using 0.5 per cent novocaine solution through a fine hypodermic needle. A small skin puncture is then made with a pointed knife. The loose tissues and the inter-spinous ligament are then infiltrated with a small amount of the same solution. A 19- or 20-gauge, flat-bevelled, spinal-puncture needle is then passed directly into the spinal canal. If this should cause any pain, a further quantity of the novocaine solution can be injected via the spinal needle along the desired path. If the point of the needle is in the canal, clear cerebrospinal fluid will drip out when the stylette is withdrawn. It is very doubtful if there is such a thing as a "dry tap". Rarely, however, the canal cannot be reached by the needle-point because of bony deformity.

The top is then broken off an ampoule of novocaine crystals (procaine hydrochloride) of the desired dosage and the spinal fluid is allowed to drip *slowly* into the ampoule up to the desired volume. The drip can be accelerated when necessary by an attendant compressing both jugular veins. The novocaine crystals and spinal fluid must be agitated by barbotage *in the ampoule* until all the crystals have disappeared into solution, making use of a 10 c.c. glass syringe and a large gauge needle. The volume is then accurately measured in the syringe. The solution is now injected into the spinal canal at the rate of 1 c.c. every five seconds without any barbotage whatever. The needle

is then withdrawn and the iodine partially washed off with alcohol. A tiny dressing is applied to the puncture wound and secured with adhesive tape.

The patient is placed on his back and the table at once tilted into 8 to 10 degrees Trendelenburg. The eyes are then covered with a cool moist towel. It is probably not advisable to use full Trendelenburg posturing within 12 to 15 minutes following the actual spinal injection. The longer it is delayed, the less will be the tendency toward unnecessarily high analgesia.*

TABLE OF SITE, VOLUME, DOSAGE

Site	Operation	Volume of Cerebro-spinal Fluid
3rd Lumbar space (between 3 and 4 lumbar vertebrae)	Lower limbs. Perineum, etc. Groin. Supra-pubic.	3.5-4.0 c.c.
	Lower intra-abdominal operations, permitting manual exploration of the upper abdominal organs.	
1st Lumbar space (between 1 and 2 lumbar vertebrae)	All upper abdominal operations. Kidney operations.	5.5-6.0 c.c.
Duration of anaesthesia desired		Novocaine dosage
20 minutes	requires	100 mgrm.
30 "	"	120 "
45 "	"	150 "
60 "	"	200 "
75 "	"	250 "
90 "	"	300 "

Note.—The above are adult dosages; allow 0.5 c.c. decrease of volume for small-framed subjects.

Caution.—Avoid using, except in robust subjects, more than 250 mgrm. novocaine in the 1st lumbar space.

COMMENT

It is realized that many authors are recommending dosages different from ours, many of which call for less novocaine and many for smaller volumes. Most of these recommended methods have received a fair trial in our hands, but nothing short of the dosages here stated has proved consistently dependable. We have therefore established, after an experience of more than 1,600 "spinals", the above routine

* It is our practice to give, by hypodermic in the anesthetized gluteal region, ephedrine, gr. $\frac{1}{2}$, as soon as the spinal injection has been completed. This is in the hope of preventing the anticipated drop in systolic blood pressure. The value of this procedure has been variously challenged, but we continue the practice because we have never had any unfavourable reaction from the ephedrine, and seldom have we had any serious drop in blood pressure.

dosages. Of course, many cases under this routine will have higher anaesthesia than necessary, and many will have much longer anaesthesia than stated in the table of dosage (the longest in our series was 2 hours and 40 minutes of actual operation in the epigastrium under 300 mgrm. novocaine), but the stated minimum results are entirely dependable.

Nausea on the operating table is very rare. However, it does usually occur in epigastric operations during the initial tugging on the stomach or gall bladder. In such cases nausea and retching can be avoided by giving light gas-oxygen anaesthesia from the time of opening the peritoneum until the stomach or gall bladder clamps have been put in place.

Pneumoperitoneum (often giving post-operative symptoms resembling "gas pains", and more often decreasing insidiously the diaphragmatic respiratory excursion) is eliminated in all "clean" abdominal operations by replacing the intraperitoneal air with normal saline, just as the last few stitches are being made in the peritoneal layer; and in all "soiled" cases by simply expelling manually as much air as possible. Normal saline is absorbed by the peritoneum in a few hours, whereas air has been demonstrated in the peritoneal cavity more than ten days after operation by Lewis,² of Toronto.

"SADDLE-AREA" ANALGESIA WITH STOVAINE

This procedure we consider particularly valuable in that it accomplishes all that a sacral block analgesia does; it is simpler, less painful afterward, and has no contraindications except the existence of a spinal cord lesion. It is, however, not suitable for rectal operations in the prone position with the pelvis raised; but our surgeons do their rectal cases in the lithotomy position. With us the stovaine technique is used, regardless of the risk factor, in all procedures requiring anaesthesia for the following classes of operation: rectal; perineal; strictly cervical; surgery of the external genitalia; and for cystoscopic and resectoscopic procedures. It induces no general body reactions and no drop in blood pressure.

THE TECHNIQUE FOR STOVAINE BLOCK

The solution used is after Barker's formula (5 per cent stovaine, in 5 per cent glucose) and comes prepared in 2 c.c. ampoules. Its specific

gravity is distinctly greater (heavier) than that of the cerebrospinal fluid.

The injection is carried out with the patient in the erect posture, sitting on the side of the operating table, with the feet resting on a stool of convenient height. The usual surgical technique is employed, and a large area of the back is prepared with iodine. The patient, with hands on knees, stoops his head and shoulders as low as possible without bending at the hips. Spinal puncture is made in the space between the 3rd and 4th lumbar vertebræ as before described, but only a drop or two of spinal fluid is allowed to escape. The ampoule of stovaine solution is then broken and the contents are drawn up into a 2 c.c. glass syringe. Any excess is discarded and the syringe is attached to the spinal needle. Then the contents are injected in a slow, steady stream into the spinal canal without any barbotage. The patient is then kept steady in the erect sitting posture for two or three minutes while the iodine is being sponged off the skin, and the dressing applied. This interval permits the heavy stovaine solution to settle to the terminal portion of the dural sac. This gives a "saddle area" of anaesthesia, and very quickly. The patient is then placed on his back with at least three pillows

supporting his head and shoulders, and can at once be placed in the lithotomy position. The dose usually employed is 1.5 c.c. of stovaine solution. This gives good analgesia for from 45 to 75 minutes. Two c.c. can be similarly used if a somewhat longer duration is to be desired.

Occasionally, with this technique, we have experienced analgesia persisting inexplicably over a period of several hours, but without any unfavourable consequences. It is probably wise (and our custom) to keep the patient's head and shoulders elevated on the stretcher and in bed for two hours following the stovaine injection.

OTHER SPINAL ANÆSTHETICS

Spinocaine (100 plus cases) has not proved dependably satisfactory in our hands. Panto-caine has not received extensive trial by us. We have administered it only a few times in order to acquaint ourselves with its technique. We have not experienced any real necessity for its use in preference to our methods described above. Other spinal analgesia preparations have not received our attention.

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✓ THE POTENCY AND STANDARDIZATION OF DIGITALIS IN CANADA

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THE importance to the public and the medical profession of possessing digitalis preparations of uniform potency has been recognized by the Health Organization of the League of Nations,¹ by the American Heart Association,² and by the Medical Research Council of Great Britain.³ Methods for the control of the potency of this product are official in the leading Pharmacopœias,⁴ and are recognized in Canada by the revised Food and Drugs Act of 1927 and by the Canadian Formulary. The purpose of this paper is to present some results of the work undertaken by the Department of Pensions and National Health to assure the physician that he can depend on the potency of the tincture he employs.

Before the Department could undertake the control of the potency of tincture of digitalis sold in Canada a study of the methods of standardization had to be made. In most methods of assay, potency has been determined in terms of cat units, frog units, gold-fish units, pigeon units, etc. The fact that such a zoological collection of units has developed is good evidence that these methods are unsatisfactory. Those using these terms did not understand the fallacies underlying them.⁵ Labels stating that products have been "biologically standardized" in animal units are misleading because such methods of test are little more than *qualitative* measurements.

In this *Journal* Baltzan⁶ has advocated ad-

ministering the drug in terms of cat units. De Lind van Wijngaarden,⁷ working with the International Standard preparation, showed that, in the extreme, one cat may require about 3.5 times as much digitalis as another, to produce systolic standstill. Therefore, it is possible to standardize two tinctures in terms of cat units and have one 3.5 times as strong as the other. Since the cat unit is not a constant quantity, it should *not* be used as a basis for calculating dosage in the administration of digitalis.

Frog units are just as unreliable. Frogs from different sources and different frogs from the same source require different amounts of digitalis to kill them. Any method which expresses the strength of digitalis in frog units actually measures the variation in frogs, not differences in potency of the samples tested. Seven cooperating laboratories,⁸ using ouabain, the U.S.P. X standard for digitalis, found that the value of the minimum systolic dose varied by 2,500 per cent, from 0.04 mg. to 1.0 mg. That is, on account of the variation in frogs, the same tincture would be called 25 times more potent by one laboratory than by another. Such has been the confusion in assaying digitalis.

The first step towards uniformity was the adoption by the League of Nations Health Organization⁹ of the International Unit based on the International Standard Digitalis Powder. One unit is equivalent to the potency possessed by 0.1 gram of the International Standard powder. The next step was the proposal of a method by Trevan¹⁰ which avoids the errors due to variations in the test animal.

This laboratory^{11, 12} has developed a modification of Trevan's method which obviates the errors previously discussed. To prove this, solutions of ouabain, a glucoside of strophanthus of known chemical purity, were prepared in different dilutions and their potency determined by the method developed in this laboratory. Some of the results are given in Table I. The values obtained by assay are remarkably near the actual value. In no case was the error greater than 4.8 per cent. Similar accuracy can be obtained with market samples of Tincture of Digitalis in comparison with the International Standard, Table II. Consistent results can be obtained in different laboratories by this method. Portions of four

TABLE I.
ASSAYS ON OUABAIN SOLUTIONS

<i>Per cent of Standard</i>		
<i>Actual Value</i>	<i>Value Determined by Assay</i>	<i>Error Per cent</i>
87.0	88.6	+1.8
86.3	86.0	-0.4
93.5	90.3	-3.4
88.0	85.1	-3.3
88.0	92.2	+4.8
94.0	91.0	-3.3

TABLE II.
TINCTURES OF DIGITALIS (MARKET SAMPLES), EACH
ASSAYED SEVERAL TIMES TO SHOW THE ACCURACY
OF THE METHOD EMPLOYED
(Potency in per cent of International Standard.)

<i>Sample</i>	<i>Potency per cent</i>	<i>Maximum Variation from mean per cent</i>
A	90.4	+4.5
	96.2	
	95.4	
	96.8	
C	82.7	+6.7
	75.6	
	74.2	
D	47.6	-2.7
	49.4	
	49.4	
	48.7	
	48.3	
J	76.2	-7.9
	69.2	
	79.8	
	75.8	
	74.6	

preparations were assayed in different laboratories with comparable results, as shown in Table III.

There are pharmacologists who have recommended the cat method in place of the frog method for the standardization of digitalis, on

TABLE III.
FOUR SAMPLES OF DIGITALIS (FOLIA PULV.)
ASSAYED IN DIFFERENT LABORATORIES
BY THE METHOD DESCRIBED (12).
(Potency in per cent International Standard.)

<i>Laboratory</i>	<i>Samples</i>			
	<i>F.L.</i>	<i>F.D.</i>	<i>B.B.</i>	<i>B.C.</i>
A	150.5	148.5	0.984	127.5
B	152.2	151.5
C	1.000	132.0

the assumption that the mammalian and amphibian hearts react differently. In a study made by several collaborating laboratories,¹³ the agreement between the frog and cat methods was very poor, a difference of 32 per cent being recorded. As a result of this and other studies, standardization in terms of "cat units" has become more common. This laboratory was unable to obtain sufficient cats, but by the same intravenous technique another mammal, the guinea pig, was used for comparison with the frog. When sufficient numbers of animals are used to account for individual variations, and a comparative standard (International Standard Digitalis) is employed, the difference between the values obtained by mammalian and amphibian hearts disappears. This is illustrated in Table IV. Five digitalis

TABLE IV.

COMPARISON OF GUINEA PIG AND FROG METHODS OF ASSAY

Potency in per cent International Standard (I.S.D.).
Five samples of Digitalis Leaf and Standard Ouabain.

Sample	Frog Method	Guinea Pig Method	Difference Per cent
I.S.D.	100	100	0.0
C.S.D.	118	116	1.7
B.C.	102	100	2.0
M.M.F.	97	97	0.0
F.D.	143	146	2.1
F.L.	147	149	1.4
Ouabain	1173	1144	2.5

samples and standard ouabain were assayed by both methods in comparison with International Standard Digitalis (I.S.D.). The greatest difference observed was 2.5 per cent. Only by expressing potency in terms of a standard digitalis preparation can such accuracy be obtained. The terms "cat" and "frog" units must be discarded.

THE POTENCY OF TINCTURE OF DIGITALIS SOLD IN CANADA

In Table V are given the results of assays in terms of per cent International Standard for tinctures from the larger manufacturers selling in Canada. In 1926, before the adoption of the regulations, the variation in potency of tinctures of digitalis sold in Canada was such that one tincture was 11 times as strong as another.¹⁵ Hence, if the physician prescribed 5 minims of tincture, the patient might have received the equivalent of 55 minims of tincture with con-

sequent misleading and, sometimes, disastrous results. Since the adoption of the regulations requiring that tincture of digitalis should conform to the International Standard of potency there is markedly less variation. Proceedings

TABLE V.

POTENCY OF TINCTURE OF DIGITALIS SOLD IN
CANADA BY FIVE LARGE DRUG HOUSES

(Potency expressed in terms of per cent
International Standard.)

Year of Survey	Potency of Samples		Ratio of Range in Potency
	Lowest	Highest	
1926	30	330	1 : 11.0
1930	63	107	1 : 1.7
1931	51	105	1 : 2.1
1932	65	125	1 : 1.9
1933	66	144	1 : 2.2

have been taken to remove from the market all tinctures found not to conform to the standard.

However, it can be seen from Table V that there is still considerable variation in potency. In 1933, as in the previous three years, outstanding manufacturers offered for sale some tinctures twice as potent as others. Nevertheless, there has been an improvement. Of the samples from *all* manufacturers assayed in 1931, only 33 per cent were within the required limits of potency, while in the following years (1932, 1933), more than 60 per cent were satisfactory. Hence, as a result of the control exercised by this Department about twice as many tinctures were found to be of standard potency in 1933 as were found in 1931. While this means that the physician is able to obtain more uniform tinctures than hitherto, attention is directed to the fact that there are still to be found tinctures which vary considerably from the standard potency.

In 1933, samples from twenty-one different manufacturers whose tinctures are sold in Canada were collected. On account of an improved method of surveying the market, this includes ten manufacturers whose products had not been previously assayed. Only 16 per cent of the samples from these 10 manufacturers were satisfactory in contrast to 60 per cent in the group whose products had been previously controlled. This emphasizes the need for standardization. As stated above, all tinctures found to be sub-standard are removed from the market. Sub-standard tinctures are not only

those which are too weak but also those which are too active. For example, in 1933, one tincture was found to be approximately one-tenth the required strength, while another was found to be twice as potent as the standard. Both of these tinctures were marked "standardized", yet one minim of the first was equivalent to twenty minims of the second.

Different lots of tincture made by one manufacturer may also show considerable variation, as illustrated in Table VI.

TABLE VI.

DIFFERENCE IN POTENCY OF TINCTURES OF DIGITALIS
OBTAINED AT DIFFERENT TIMES FROM THE SAME
MANUFACTURER

(Potency in terms of per cent International Standard.)

Mfr. A.	Mfr. B.	Mfr. C.
74	63	57
105	30	87
87	61	65
144	127	93
172	71	111
	58	91
		93

One difficulty of the manufacturer in producing and marketing tinctures of uniform strength is the fact that deterioration may occur quite rapidly.¹⁴ No satisfactory method of preventing this loss of strength has been proposed. *Dried leaf preparations, such as capsules, are not subject to this disadvantage*, and from the standpoint of potency and dosage are to be recommended in preference to the tincture.

As Baltzan⁶ has pointed out, the number of different digitalis products on the Canadian market is becoming confusing. There is often no way of expressing the strength of one product in terms of another. There are nearly as many different ways of expressing potency as there are different preparations. For the protection of physician and patient, there should be uniform potency in digitalis preparations on the market, and one recognized method of expression.

Uniformity can best be obtained by adopting the International Standard Digitalis preparation and by the use of a reliable and accurate method of assay. It is recommended that *other digitalis preparations*, as well as the tincture, be standardized in terms of International units and assayed by a method such as that described.^{11, 12} The physician should become accustomed to ad-

ministering the drug in terms of *International units* in place of the inaccurate and misleading animal units. In the revised Food and Drugs Act of Canada (1927), the Canadian Formulary, and the British Pharmacopœia (1932) the International Standard unit is official. Fifteen minims (approximately one cubic centimetre) of tincture is equivalent to one International unit.*

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* Since the foregoing article was written, a discussion on the standardization of digitalis has appeared in the *Journal of the American Medical Association*. In the first communication¹⁶ the "Digitalis Committee" advocates the cat unit of potency. The Chairman of the Subcommittee on Biological Standardization of the U.S. Pharmacopœial Revision Committee, Dr. C. W. Edmunds, in the second communication¹⁷ has very ably stated the objection to the adoption of the cat unit. We agree with Doctor Edmunds that the cat unit will only lead to confusion.

As previously stated, the most logical unit is the "International Unit" which is a measure in terms of digitalis, the drug itself, and is independent of the method of assay and of the kind of animal employed. This is one reason that the Canadian Regulations specify the International unit. When such a comparative standard preparation is employed much is accomplished toward solving the "dilemma." The introduction of a new test animal¹⁸ only adds to the confusion.

It is agreed that the physician should possess digitalis preparations of uniform potency, but the recommendations of the "Digitalis Committee" will not render this service to the medical profession and their patients.

THE USE OF MAGNESIUM SULPHATE IN CANCER

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IN presenting the results obtained by the use of magnesium sulphate in the treatment of carcinoma it is not with the intention of making any claim either for curative or palliative value but rather in the endeavour to stimulate interest and render further trial and observation possible.

At the Montreal General Hospital the end-results in the majority of malignant lesions of the pharynx, base of the tongue, œsophagus, and in extrinsic laryngeal cases have been most disappointing, whether the cases were attacked by surgery, electro-coagulation, radium or deep x-ray. The same may be said for the results published by other clinics where the average malignant case is first seen in a more or less well advanced condition. Even by improving our present technique, or by acquiring larger quantities of radium, little further of practical value can be offered to this class of patient.

What cancer is, what the "X" underlying the cause of cancer is, has yet to be answered. It is not even a certainty whether cancer is a purely local condition or a systemic disease, but I believe that even if a malignant growth be thoroughly and completely destroyed, whether by surgery or by irradiation, that "X" is still present in that patient and he remains in the same category as he was before the tumour manifested itself, namely, a potential cancer subject. No assurance, and certainly no guarantee, can be given to any cancer sufferer after he has submitted himself for treatment that he will be immune from future recurrence.

My attention was first drawn to the possible effect of magnesium sulphate for the treatment of carcinoma by the fact that at the Radium-hemmet in Stockholm, Sweder, it is given as a routine treatment for leukoplakia, ordinary warts and papillomata, which are recognized precancerous conditions. To quote from "The Technique in the Treatment of Tumours at Radium-hemmet, Stockholm," by E. Berven, J. Heyman and R. Thorams—"In recent years we do not give

radium treatment, but try at first medicinal treatment. As a rule we give 1 gr. of magnesium sulphate three times daily, and the patient is kept on this for three months. The leukoplakias are markedly reduced on this treatment. This treatment has been based on the experience gained from the effect of $MgSO_4$ on papillomata and ordinary warts."

The multiple warts on the hands which occur epidemically in children respond in a remarkable degree to treatment with $MgSO_4$ internally. The treatment must be continued for 2 to 3 months and must be carefully watched. In about 40 per cent of the treated cases the warts are completely absorbed, and in other cases the majority of them disappear while the mother-warts themselves remain.

Many references may be found in the literature regarding magnesium sulphate and other salts, particularly sodium, calcium and potassium, regarding their relationship to malignancy. As Shear,¹ of the Harvard Medical School, has recently pointed out, there is so much contradictory evidence up to the present time that no conclusion can be drawn.

Contributions by Brumpt² and by Schrumpf-Pierron³ show that carcinoma is approximately ten times less frequent in Egypt than in European countries, and these authors endeavour to prove that this is intimately linked with the richness in magnesium of the soil and water.

If relatively small doses of $MgSO_4$ have a beneficial effect in the treatment of pre-cancerous conditions, as demonstrated at the Radium-hemmet, Stockholm, and, secondly, if the observations made by Schrumpf-Pierron and others are correct, that $MgSO_4$ is present in the soil, and consequently the daily consumption of this salt in the drinking water and foodstuffs prevents the occurrence of cancer, then we might inquire whether larger doses would have any beneficial effect upon the mature cancerous tumour. For these reasons I determined to try its

effect upon some of our apparently hopeless cases.

The first three case reports I shall give in some detail. Several others have been given a trial with the salt and have shown little or no improvement and have followed the usual course, particularly those with bone involvement.

CASE 1

E.E., male, aged 40 years (Hosp. No. 877-33) was on February 12, 1933, admitted to the Montreal General Hospital.

Complaints.—Obstructed nasal breathing; lumps on the neck. The symptoms were first noted 5 months previously.

Family history.—Mother died of cancer of the breast; otherwise, irrelevant.

Present condition.—A large sloughing mass completely filled the nasopharynx. Nasal breathing was impossible. The cervical glands on both sides were enlarged, a large fixed mass on the right side, extending downwards from the mastoid process. Multiple discrete movable glands present on both sides of the neck, from the size of olives to that of peas.

February 13, 1933. Biopsy from the nasopharynx; pathological report—epidermoid carcinoma, Broder type 3.

February 15, 1933. Columbian paste radium collar applied. A full erythema dose was given.

March 6, 1933. 50 mg. radium tube to the nasopharynx for 20 hours.

March 11, 1933. Discharged from the hospital; general condition poor. He has lost 30 lbs. in the past 6 weeks; weight, 130 lbs.

March 29, 1933. Has had three 1/6 erythema doses of deep x-ray. His general condition was so poor that further x-ray treatment was considered inadvisable. Morphine, 1/4 gr., three times a day.

April 2, 1933. Began MgSO₄. May 3, 1933. General condition much improved. May 22, 1933. Glands still palpable, but greatly reduced in size. Morphine, 1/4 gr., at night only.

June 20, 1933. Weight, 141 1/2 lbs. He was wearing his usual collar for first time.

August 28, 1933. Nasal breathing normal. Weight, 158 lbs.

November 3, 1933. He had returned from a trip to England. Weight 176 lbs. The mass was still palpable on the left side of the neck. A further biopsy made from the granulation tissue in the nasopharynx, showed epidermoid carcinoma, Broder type 3.

February 19, 1934. Weight 179 lbs. Nasal breathing free; gland still palpable on the left side of the neck; no complaint of pain or discomfort.

CASE 2

Mrs. C.P., aged 54 years, had been under observation at the Montreal General Hospital, Ear, Nose and Throat Clinic, since August, 1928. At that time a hard tumour was present involving the left ethmoid and antrum, occluding the left nares and pressing the nasal septum to the opposite side. She received varying doses of deep x-ray therapy.

June, 1930. She had a large hard mass completely obstructing the left nares and protruding anteriorly through the vestibule. The posterior choana was obliterated. The soft tissues over the bridge of the nose and left lachrymal were involved.

November, 1930. Weight, 144 lbs.

Throughout 1930, 1931 and 1932 she was given repeated treatment with radium needles, radium tubes in the left maxillary antrum, radon seeds in the soft tissues over the bridge of the nose, and broken doses of deep

x-ray. The tumour was reduced in size and her nasal breathing was seemingly normal.

December, 1932. She was readmitted to the wards suffering from a bilateral suppurative otitis media, following an attack of influenza.

January 5, 1933. Simple mastoidectomy was performed upon the left side.

January 9, 1933. Ligation of the left internal jugular vein.

February 5, 1933. Discharged. The nasal passages were very foul and filled with foetid crusts.

March, 1933. Treatment with MgSO₄ was begun.

June, 1933. The mass in the nares showed regression. The foetor had disappeared. Weight, 149 lbs.

July 7, 1933. A sequestrum was found under the left lachrymal area with a small fistula.

August 11, 1933. Weight, 150 lbs.

September 8, 1933. Weight, 154 lbs.

October 30, 1933. She stated that for the first time in three years she had had no pain or discomfort. There was, however, foetor from the sequestrum.

February 16, 1934. Weight, 156 lbs. She stated that she had not felt so well for years. Nasal breathing free; a small sequestrum still present.

CASE 3

J.N., male, aged 65 years, single, clerk, on December 6, 1932, consulted the Ear, Nose and Throat Out-patient Clinic at the Montreal General Hospital.

Complaint.—Hoarseness for three days. Indirect examination showed a definite tumour mass with ulceration in the area of the right arytenoid and aryepiglottic fold. Provisional diagnosis.—Extrinsic carcinoma of the larynx. A Wassermann test was reported negative.

December 6, 1932. Biopsy.—Pathological report, adenocarcinoma, Broder type 4. Operative interference was considered inadvisable, likewise irradiation. He reported at the clinic twice. A fungating mass rapidly increasing in size.

February 28, 1933. Growth had increased considerably. There was difficulty in swallowing. Admission for gastrostomy was recommended.

April 3, 1933. Emergency tracheotomy.

April 21, 1933. He was discharged from hospital wearing a tracheotomy tube and able to swallow semi-fluids.

April 28, 1933. Treatment with MgSO₄ was begun.

June 2, 1933. Feeling much better.

June 20, 1933. Weight, 168 lbs. He gained 4 lbs. in 3 weeks.

July 4, 1933. No apparent change in size of tumour, but it was cleaner. He was swallowing well, and could breathe with the tube blocked for 10 minutes.

August 18, 1933. Very little slough or mucus present.

September 12, 1933. Larynx clean.

September 26, 1933. Larynx clean; no difficulty in swallowing.

October 17, 1933. The tumour was markedly reduced in size; swallowing ordinary food. He could breathe comfortably without the tube. Weight, 204 lbs. He was taking long walks daily to reduce weight.

October 30, 1933. Weight, 206 lbs. No discomfort either in breathing or swallowing.

February 16, 1934. No symptoms of pain. Weight was being maintained; no difficulty in swallowing. He breathed with the tracheotomy tube corked for an indefinite period.

CASE 4

Mr. M., aged 76, with cancer at the base of the tongue, referred by Doctor Bazin. Fixed cervical glands coherent to the mandible. He had had radium applied while in Vancouver. He began MgSO₄ in June, 1933, with definite relief from pain and salivation, but did not tolerate the salt well. Gastrostomy done in August. He died late in October from a sudden cardiac attack.

The method of administration has been purely empirical up to the present. The patient has been given 3 i to 3 ii MgSO_4 in water by mouth, 2 to 3 times daily, depending upon the bowel tolerance; that is allowing 3 to 4 loose stools daily, but avoiding purgation or distressing symptoms. The salt may be given with milk, orange juice, or, as at the Montreal General Hospital, in the form of a mixture flavoured with elixir of pepsin and camphor water. Some of our patients become very tolerant to the salt, and the quantity can be rapidly increased. Recently we have been using a 25 per cent hypotonic solution of MgSO_4 intramuscularly, but it is too early to make any comment upon this method of administration.

In conclusion, I wish again to state that no claim can be made as to curative value, but in certain cases treated we have noted: (1) retrogression in the size of the tumour and clearing

of the slough; (2) relief from pain; (3) increase in body weight; (4) very marked improvement in the mental attitude of the patient; (5) the induction of a feeling of well-being.

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WHY LATE DIAGNOSES IN MALIGNANCY?

(AN ANALYSIS OF TWO HUNDRED LATE DIAGNOSES)

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THE object of this analysis is an examination of some of the many factors that enter into the situation of late diagnoses in malignancy. The data presented have been secured by questioning 200 consecutive patients with malignancy who have presented themselves with evidence of a late diagnosis. For the purposes of this analysis, cases have been considered late whenever the primary lesion was massive, when ulceration and mixed infection obtained, when invasion of adjoining tissues was definitely apparent, when the primary or secondary glandular areas were involved, or whenever, as the result of the condition, definite constitutional disturbance was in evidence.

That late diagnoses in malignancy not only lend complexity to treatment but also perpetuate unnecessary terminal disaster is the emphatic testimony of all those who labour in this particular field of medical endeavour. That early diagnosis could help in saving many lives now unnecessarily lost, that it could prevent untold suffering, and also that it could effect a tre-

mendous economic saving in lessening treatment costs, hospitalization periods, and post-treatment invalidity, is not likely to be questioned by any who are at all familiar with the existing situation.

Of the total cases examined in this series, there were 62 involving the breast, 52 of the uterus, 42 of the gastrointestinal tract, 38 of the lip, 18 of the skin, 13 of the buccal cavity, 12 genito-urinary, 12 of the jaw, 9 of the ear (pinna), 8 of the eye (cutaneous), 7 of the lung, 5 of the nose (cutaneous), 3 of the chest, 3 of the thyroid and 3 of the tonsil; also 8 cases of sarcoma. Of this total material 200 were selected as definitely late in finally reporting for diagnosis and treatment.

As to why there should be such a situation of tardy recognition and late treatment, it was early apparent that practically all late cases could be classified under certain rather definitely circumscribed headings. Under these headings or combinations thereof, could be found the explanation, and quite probably they also represent

the universal situation in this regard. Decidedly illuminating are these answers, for when questioned in relation to the delay almost invariably the patients gave, in substance, one of the following types of answers. There were 413 explanations in the 200 cases considered (explanations are usually multiple).

1. "It has never given me any pain". (in 32, or 7.7 per cent).
2. "I didn't think it was serious". (in 64, or 15.5 per cent).
3. "I have long intended having the condition examined, but have just kept putting it off". (in 25, or 6.05 per cent).
4. "I felt I couldn't afford to have it attended to". (in 39, or 9.44 per cent).
5. "I didn't know anything was wrong". (in 26, or 6.3 per cent).
6. "I thought the condition was just natural". (in 44, or 10.5 per cent).
7. "I was afraid it might be cancer". (in 25, or 6.05 per cent).
8. "I was afraid of an operation". (in 21, or 5.08 per cent).
9. "I never thought of cancer". (in 22, or 5.3 per cent).
10. "I had been previously advised that nothing was wrong". (in 25, or 6.05 per cent).
11. "I have been trying various treatments, thinking it would get better". (in 20, or 4.8 per cent).
12. "I thought it was just indigestion, piles, constipation, or some such commonplace condition". (in 70, or 16.9 per cent).

Of the total explanations of late diagnoses, "absence of pain" (No. 1) is recorded as a reason in 7.07 per cent of the answers. Simple procrastination (No. 3) accounted for 6.05 per cent. Fear (Nos. 7 and 8) accounted for 11.13 per cent. Misdirection (Nos. 10 and 11) accounted for 10.13 per cent. Financial impediment (No. 4) accounted for 6.3 per cent. Ignorance (Nos. 2, 6, 9, 12) in relation to the significance of departures from normal physiological function, and common danger signals in association with self-diagnosis accounted for 48.3 per cent. From these answers it is readily seen that a combination of undesirable factors, to no small degree preventable, account for the inevitable terminal disaster. When we recall that approximately 75 per cent of all cancer cases come under treatment with a late diagnosis, and, as a direct consequence, with a hopeless prognosis, when we recall that it is only in the early cases that we are entitled to be reasonably hopeful as to the outcome of our treatment, we more fully realize the fact that the sheet anchor of our present endeavours largely rests upon a basic consideration—early recognition.

In an enquiry of such nature as now conducted, in addition to the specific information

sought, there are constantly in evidence many intensely interesting sidelights and observations which are of material value in assisting us to more thoroughly appreciate the problem that confronts us. After reviewing the total evidence presented by this most unfortunate group of patients, there is perhaps justification for presenting the following deductions.

In the series under consideration it is perfectly obvious that not only is the average patient not cancer-minded, but neither is he in any reasonable measure familiar with the serious significance of those common danger signals that the enlightened profession immediately interprets as such, that definitely suggest the possibility of malignancy, and afford a positive indication for immediate and considered action.

In relation to late diagnoses it has been suggested that the public is apathetic, careless, unnecessarily ignorant, and does not reasonably strive for enlightenment. Not only does the present series not give substantiation to these conceptions, but one gets the definite impression that the average individual is anxious to know the facts, but is at a distinct loss to know where to get the type of information, simply stated, that will provide assurance of definite direction.

Because of the fact that the public is familiar with the terminal pictures in malignancy almost exclusively, it apparently has logically followed that popular conceptions in relation to malignancy are based on these particular observations. Since early symptoms bear little resemblance to those seen in advanced cases, definite misconception cannot but be expected. Particularly misleading is the conception that pain is a necessary accompaniment of malignancy. Because of this distorted picture that the public visualizes as portraying malignancy, wide-spread misconception also obtains in regard to what constitutes appropriate treatment in the various stages of malignancy's evolution. To no small degree this unfortunate situation accounts for the element of definite fear that constantly surrounds malignancy, and in consequence it most effectively functions in retarding timely action in countless cases. Lord Moynihan gives point to this basic factor when he says, "Fear of a cancer diagnosis and fear of the indicated treatment cannot but make for disaster, but fear of a late diagnosis is legitimate and should be encouraged."

That a very large percentage of women are totally unfamiliar with the serious significance that attaches to departures from normal menstrual function appears perfectly obvious. It is also evident that lumps in the breast frequently escape recognition over prolonged periods, and, even when discovered, unless accompanied by pain, these abnormal findings are not infrequently ignored as matters of little or no consequence. It is this disastrous situation that accounts for the fact that out of our total death rate from malignancy nearly 20 per cent is found in these two groups. (In 1931 in Canada there were 4,828 deaths in women from cancer. Of this number there were 1,809 deaths from cancer of the generative organs).

That self-diagnosis and contempt for apparently trifling symptoms are the most common errors that frequently lead to terminal disaster is well recognized. That more or less constant familiarity with not altogether dissimilar symptoms that have not eventuated in disaster accounts for the false security that patients so often entertain is possibly not equally well recognized. Only in adequate education shall we find a solution for this most disastrous impediment to earlier diagnoses.

It is thoroughly appreciated that the well-intended advice that is so often tendered to the cancer patient by ill-advised friends very

frequently contributes to unfavourable end-results because of the definite misdirection that is provided. Too often, we lose sight of the fact that, seeing only the occasional cancer case and being largely non-conversant with modern diagnostic and treatment procedures, not infrequently medical men similarly contribute to definite misdirection. Because of this unfortunate situation the urgent necessity for public and professional education in relation to cancer is again accentuated.

When we recall that approximately 30,000 Canadians are annually afflicted with cancer, and that one-third of this colossal number, to no small degree unnecessarily, are yearly relieved of their suffering by death; when we recognize that it is only in early diagnosis that we can offer the patient a reasonable prospect of cure, we more fully realize the necessity for at once instituting a type of organization that will effectively function in assisting to remove the many unfavourable factors that are constantly at work in perpetuating late diagnoses.

The cancer victim's greatest enemy is ignorance. The complete eradication of this disastrous element must be our first objective if we, as a profession, are to function effectively in an organized endeavour to minimize the menace that the ever-rising incidence of malignancy is imposing upon the people of this country.

A CASE OF ASTHMA DUE TO MAY FLIES (EPHEMERIDA)

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THERE are so many substances which may set up sensitizations that the tracing of the one or more responsible for allergic symptoms in a given case may call for a good deal of investigation. In most cases, however, the sensitizing agents are either clearly indicated in the history, or are confined to a comparatively small group, particularly when they are of the inhalant type, such as the pollens and the epidermals. Amongst the latter we usually think first of such common excitants as horse dander, and the hair or feathers of other domestic animals. But it should be realized that all epidermal material is a potential sensitizing agent, no matter from what source it is derived, and we should there-

fore expect occasionally to come across cases of unusual origin. It seems to be a matter of sufficient exposure to the given substance in a susceptible individual.

Some of the less usual epidermal excitants recorded are, humming birds, butterflies, bed-bugs, and bees. In the following case report I shall give details of yet another insect which has been implicated in causing asthmatic attacks.

CASE REPORT

In mid July of this year the patient, a man of 44, presented himself (referred to me through the courtesy of Dr. Lochead) with all the symptoms of bronchial asthma, accompanied by some coryza and sneezing, although when I saw him his attack was nearly over.

He came from North Bay, Ont., on the shore of

Lake Nipissing, where he worked as an expressman with the C.P.R. His history showed that during the past five years he had suffered from these asthmatic attacks in late June and July, for a period of about five weeks each year. Both before and after this time he was perfectly free of any symptoms. He found, however, that when he travelled some distance out of North Bay, either west to Fort William or east to Montreal, his attacks abated, but as soon as he got back to North Bay they returned.

His family history showed that one brother was subject to hay-fever, and one sister was hypersensitive to celery. His personal history contained nothing else of special note.

His own view was that his trouble was due to the May flies, of which he said there were incredibly large numbers in North Bay, but as it was necessary in any case to eliminate other more likely possibilities, I spent a good deal of time testing him with the summer pollens and the ordinary foods. When, however, I found him to be entirely non-reactive to any of these I began to think of his own explanation, *i.e.*, the May flies.

Samples of the flies were sent down from North Bay, and I tested them on him both by the conjunctival and the cutaneous scratch test. A mere flick of the caruncle with the wing of a fly produced

that he was better when he came down here, but of course that might have been accounted for by his staying in the city away from the breeding places of flies. I obtained no May flies in my random sample, but they must undoubtedly occur here, and probably in large quantities.

TREATMENT

I attempted desensitization, but circumstances made it a rather hurried procedure. A rough extract containing the epidermal structures of the May fly was made by maceration of a handful of the flies in a buffered solution of glycerine and saline, with metaphen as a preservative. Filtration of this produced a clear brown fluid. Its nitrogenous content was not determined, but as it produced powerful reactions on the patient by cutaneous tests, I regarded it as of high concentration, and diluted it by successive stages to a strength of 1:100,000. Tests with this dilution gave only very mild reactions, and I therefore began treatment with it. Injections were given at two-day intervals, beginning with 0.2 c.c. of the 1:100,000 dilution and increasing fairly rapidly until the 1:100 strength was reached. He developed one attack of asthma, but no other general reactions. There was a moderate local reaction after each injection. Adrenalin was given with the stronger doses.

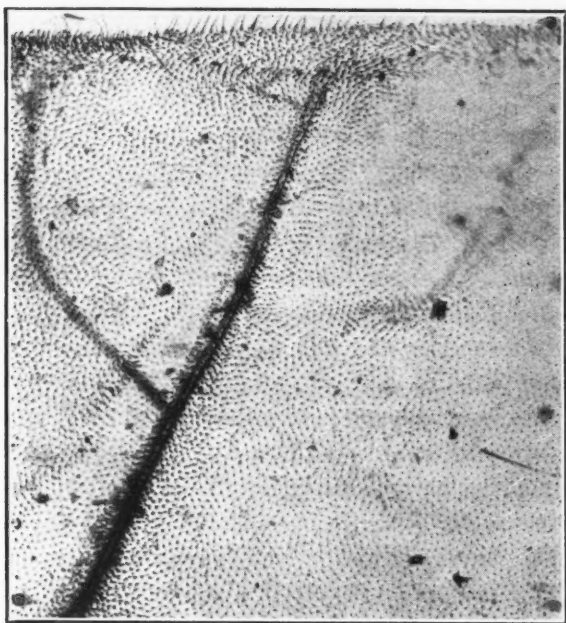
He went back to North Bay in two weeks' time, and reported further attacks of asthma, but less severe in nature. A week later he reported complete freedom, but the local fly season was then practically over, according to him, and the cessation of his attacks was to be expected in any case. He is continuing his treatment, but it will not be until next year that its efficacy will be put to the test.

The specimens of flies sent down from North Bay belonged to the Order Ephemera, and are known popularly, and indiscriminately, as May flies, shad flies, or lake flies. One American writer even gives them the title of "Canadian soldiers". Professor E. M. DuPorte, of MacDonald College, has been kind enough to identify them for me, and to give me some idea of their life history.

The flies, as such, have only a few hours' existence, theirs being indeed but a "transitory life"; the name of their Order has been appropriately chosen. They leave the water, where they have spent from one to three years (depending on the species) in the nymph stage, crawling on the bottom or swimming, and rise or crawl out on the bank with wings fully developed, usually coming out in the early twilight. Their few hours are then spent in just four more events; in moulting; in a whirling dance along with swarms of other flies; mating; and laying their eggs. These they drop into the water, and soon after fall dead. They take no food, and die without seeing a sunrise. The mouth has become so rudimentary that it cannot be used for feeding, and the stomach is merely distended with gas, helping to sustain the flight.

The May fly is the only insect which moults after it has acquired wings. These cast-off garments probably play their part in scattering the hair and epidermal scales responsible for asthmatic symptoms, although most of this material must come from the bodies and wings of the immense numbers of the insects which may be washed up on the shore, or as they lie about on streets, gardens, etc. High winds may carry them inland for a considerable distance. My patient used to notice them flocking into his baggage car, attracted by the light.

Cases exactly similar to this one have been reported in the United States by Figley³ in 1929, but this is the first recorded in Canada. The series reported by S. J. Parlato,² of Buffalo, was



Microphotograph of dried May fly's wing, showing hairs along edge and on surface.

in a few minutes a violent reaction, with intense engorgement, itching, and lachrymation, and by the next morning the eye was nearly closed. The scratch test was done by soaking a wing in decinormal sodium hydrate and scratching through it into the arm. This produced a similarly sharp local reaction, which persisted for 24 hours.

There seemed to be little doubt then as to at least the main source of his asthma.* In further confirmation, I collected specimens of various flies, shad flies, dragon flies, and another unidentified species, from the shores of the St. Lawrence and Lake St. Louis in this neighbourhood, and tested each one of them in the same way on him, but using the scratch test only, as the conjunctival method seemed to me to be unjustifiably severe. None of these produced any reaction on him, beyond a very mild response from the shad fly. This was in keeping with his statement

* The Prausnitz-Küstner test was not carried out.

caused by the caddis fly (Trichoptera), an entirely different species, although it is popularly included under the vague heading of "shadfly", as are so many others. My patient was non-reactive to the variety in this district at any rate.

There is no other record in Canada of hypersensitiveness to the May fly (Ephemera). It is more than likely, however, that other similar cases exist in this country and will be detected,

especially amongst dwellers on the shores of the Great Lakes and the St. Lawrence.

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Case Reports

A CASE OF TYPHOID FEVER WITH
HÆMORRHAGIC ONSET

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Certain apologies are due for presenting a case of typhoid fever, but because of the comparative infrequency of this disease nowadays in a civilized community, and because of some unusual features connected with our case, we feel justified in recording it.

Case No. 25879. Miss J.L., aged 24, a French-Canadian, single, was admitted on August 20, 1933.

History of present illness.—On August 19, 1933, at about 3 a.m., the patient suffered a sudden profuse nose-bleed. A physician was consulted, who packed her nose. The bleeding, however, continued, and the patient was admitted to the hospital. A few days preceding this incident the patient complained of a cold in her chest, but was able to continue her work (in a biscuit factory). This was the first time in her life that she had developed a nose-bleed of such severity. She denied any injury to the head. She did not notice any abnormal bleeding *per vaginam*; no bleeding from the gums; no melæna; no hæmaturia. There was no family history of a hæmorrhagic diathesis. The patient's daily diet did not suggest the possibility of avitaminosis.

Past and family history.—Negative.

Physical examination.—Temperature 98°; pulse 140; respirations 20. The patient was a fairly well-developed, well-nourished white female, rather pale, and did not appear acutely ill. On the twenty-second day of August (two days after admission) she looked very ill,

and markedly anæmic; no icteric tinge. The tongue was dry and coated. The pulse was relatively slow, soft, and dicrotic. Temperature 103.6°; pulse 100.

The skin showed some acne; in the neighbourhood of the right elbow and on both feet and legs there were numerous small purpuric spots; in the middle of the left tibia there was a large ecchymotic area; also a few similar spots on the thighs. The left nostril was found packed. There was no apparent bleeding from the buccal mucosa. The teeth were carious. The tonsils had been removed; anterior pillars injected. A few small palpable lymph glands were found in the left axilla; no other lymphadenopathy.

The heart showed no enlargement; a thumping first apical sound and a soft systolic murmur. The aortic second sound was accentuated; blood pressure, 102/78.

The chest showed a little lagging of the left upper part; an impaired note was found over the left infraclavicular area; auscultation revealed no abnormalities.

The abdomen was of normal type; there was no distention or tenderness; it was freely movable. The liver and spleen were not palpable. The fundi revealed no abnormalities.

Hess's capillary test was positive in less than ten minutes.

Laboratory data.—Urine (catheterized specimen) orange-coloured; clear, acid; specific gravity 1030; albumin plus; sugar 0; a few granular casts and an occasional white blood cell and red blood cell.

Blood.—Hæmoglobin 75 per cent; red blood cells 4,680,000; white blood cells 8,200; differential count: polymorphonuclear neutrophils, 83 per cent; eosinophiles, 0 per cent; lympho-

cytes, 15 per cent; monocytes, 2 per cent; many "stab" forms, slight shift to the left. Platelets, 142,700; bleeding time, one hour twenty minutes; coagulation time, three minutes; retraction of clot, nineteen hours.

Blood-Wassermann and Kahn tests were negative.

X-ray of the chest and heart revealed normal findings.

It was thought at that time that the patient suffered from (1) a purpura of idiopathic type, with fever resulting from the nasal packing, or (2) an overwhelming blood infection with purpuric manifestations. The packing was removed on August 24th, but the fever continued. The patient looked much duller, more anæmic; new hæmorrhagic spots appeared over the left forearm. There were no rose spots; the spleen was not palpable. On August 25th bleeding from the nose ceased spontaneously. On the following day a small transfusion (300 c.c.) was given with no apparent reaction. August 27th a few rose spots appeared on the abdomen and chest; the spleen was not felt but the splenic dullness was enlarged. The diagnosis was finally clinched when a positive Widal test (in a dilution of 1:40, 1:80 and 1:160) was obtained.

The patient was placed on routine typhoid orders. She ran a typical course and on the twenty-third day of the disease the fever began to remit; the temperature became normal on the twenty-eighth day. On the thirty-second day the patient suffered a relapse. At this time the spleen was distinctly palpable, but no rose spots or new purpuric spots made their appearance. On the 39th and 41st days of her illness the patient suffered two intestinal hæmorrhages (about 500 c.c. each). Following this, she began to improve steadily. On the fifty-first day of her disease the temperature and pulse became normal and remained so since. From October 31, 1933, the stools and urine remained negative for *B. typhosus* and the patient was discharged in good health on November 16th.

It may be mentioned that before her discharge the patient's urine and blood revealed entirely normal findings (October 31, 1933).

DISCUSSION

Three unusual features are noted in connection with this case. (1) First with regard to the onset. The patient took sick more or less abruptly, with a very severe hæmorrhage from

the nose, as a result of which she finally required a transfusion. In the Johns Hopkins series of 1,500 cases¹ nose-bleeds occurred in 323 cases. The most common features—headache, anorexia, diarrhœa and abdominal pain—were not found in this patient. (2) Very early in the course of her illness the patient presented many features of purpura hæmorrhagica. In 38 cases of the above-mentioned series purpuric spots were observed; however, in 29 of these cases rose spots were noted first, and these later became hæmorrhagic. Only in 9 cases was the rash hæmorrhagic from the start. It is apparently quite a rare form of the disease. Thus Liebermeister noted the hæmorrhagic form in 3 cases among 1,900 cases; Uskins, 4 among 6,318 cases; and Curschman had 6 cases. The bleeding is frequently from the nose, gums and intestines; less often it is from the lungs, kidneys or uterus; petechiæ may be seen in between the rose spots. J. H. Pratt's analysis of 258 cases of purpuric disease (Osler's System of Medicine, Vol. 5) shows the following distribution: essential purpura 52; symptomatic 64; non-thrombocytopenic 142. In the symptomatic group the highest number (10) was due to typhoid fever. (3) Finally our patient had a relapse, and during it two severe hæmorrhages from the intestines. Whether these were part of her hæmorrhagic diathesis or would have occurred anyway is merely a matter of speculation.

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A CASE OF DIABETES WITH EXHAUSTION TREATED BY "CORAMINE"

By F. W. TICKETT,

Toronto

Because of the unusual character of the following case, and not having been able to find one like it in the literature, I feel that it is of sufficient interest and importance to be reported.

During the summer months from eight to ten thousand people visit the beach at Centre Island, Toronto, daily, when the weather is fine. As attending physician, I am called in for the usual complaints which go with this type of practice, as well as for the various emergencies such as drowning, heat-exhaustion, sunstroke, etc. In the middle of August, 1933, I was summoned to the beach about one o'clock in the afternoon on a rush call to attend a man reported to be dying.

Thinking that it was the usual case of drowning, heat-exhaustion, or a post-prandial condition, I made sure of having a few ampoules of pyridine-b-carbonic acid diethylamide 25 per cent solution (coramine) in my bag, as on a number of occasions I experienced quicker and more lasting results from it than from the usual stimulants one uses in such emergencies.

Upon arriving at the beach I found a young man, well-nourished, in a serious comatose condition. He was slightly cyanosed, hands and feet cold and livid, pulse hardly palpable, and respiration rapid and loud, but not stertorous. No friends or relatives were at hand who might have given me any information as to what had happened, or as to his previous history. Because the patient appeared to be dying, I felt that an immediate stimulant was needed. I injected, in one dose, intravenously, 6 c.c. of pyridine-b-carbonic acid diethylamide (25 per cent), and within two or three minutes the patient had regained consciousness and was able to answer questions. This revealed that the young man was 24 years of age and a diabetic who had been under treatment for the past three years. At about 10 a.m. that same day he had taken his customary dose of insulin, after which he went to the Island, arriving at about 11 a.m. After going for a swim he rested on the sand for some time. He was emphatic in his statement that he had not over-exerted himself, and did not believe that he had over-exposed himself to the sun's rays. His skin did not show any signs of excessive redness which might have led me to believe that I was dealing with a case of sunburn, in which through the breakdown of the damaged skin area autointoxication may be provoked by the endotoxins liberated, resulting in coma. He had also put off taking his mid-day meal beyond his usual time. He stated that while resting he felt giddy and weak and then fainted, recovering consciousness, as noted above, on the administration of coramine. In a couple of hours' time the man was well enough to return home, and I had him continue the diabetic regimen he had been following. I feel that without the aid of pyridine-b-carbonic acid diethylamide he probably would have died, when his diabetic condition would have been discovered only at autopsy.

I consider that I dealt here with a case of diabetic coma initiated by over-exertion (in

spite of the young man's denial), this condition having been rather hard to diagnose from the symptoms evidenced and without knowledge of the previous history.

The stimulating action of pyridine-b-carbonic acid diethylamide on the medullary centres is well known. Dr. T. J. Orford has reported¹ a case of poisoning with a barbiturate, and according to him, Wood,² Reese,³ and others, coramine should be used as the antidote in accidental, experimental and suicidal intoxications induced by agents with narcotic action. However, a central paralysis is not the only danger with many poisons; the heart and blood vessels often fail, and it is in such a periphero-central disturbance that coramine seems to have acted in this case almost as a life-saver. Broadly speaking, diabetic coma, uræmia, and acidosis due to excessive fatigue are also poisonings, endogenous toxicoses, and it would appear to be worth while investigating whether pyridine-b-carbonic acid diethylamide, besides acting selectively in poisonings by narcotic and hypnotic substances, also has an antidotal effect on intoxications in general, with the exception, of course, of poisons provoking convulsions.

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ACUTE LIVER FAILURE

BY HOWARD L. SIEG, B.Sc., M.D. AND
ERIC MASSIG, M.D.,

Regina

Baby W.H., (No. 1605), aged 3½, was considered perfectly well by his parents until two weeks before I (H.L.S.) saw him. At that time his parents first noticed a slight yellowish tint of the scleræ and of the skin. He seemed in good health, played all day out of doors, and made no complaints. He ate his food well, which consisted of a good variety of garden vegetables along with other articles of a well balanced and simple diet. During the next two or three days he became more deeply jaundiced, refused all food, and became listless. The urine was noticed to be deep orange in colour and the stools from then on became lighter, until they were almost

white. He remained in this state, still spending most of his time out of doors, until the day before admission. He was more listless than usual that day and vomited blood. On closer questioning, the mother was not certain that the blood was vomited, because she had looked into his mouth and had seen blood behind his tongue and then thought it might have come from his nose. Further, the blood was fresh and not dark or clotted.

Family history.—A brother eight months of age; had always been well; raised on the bottle, with plenty of orange juice and cod liver oil; had never had any jaundice; the liver and spleen appeared normal in size; neck glands slightly enlarged. The mother remembered having to stay out of school a whole year with jaundice, otherwise she had always been well. The father had had jaundice as a baby; had never been sick otherwise and denied venereal disease. The Wassermann test of the father and mother was negative in each case.

Physical examination.—The child was well developed and well nourished, deeply jaundiced, and appeared quite sick and drowsy. He showed no interest in the examination and did not respond to questions. The hair was beginning to take up the yellowish colour. Several petechial hæmorrhages of the mucous membrane of the roof of the mouth were observed, but none of these in the skin. The heart and lungs were normal. The liver was not enlarged, and possibly diminished, for a child of this age. The spleen was barely palpable and seemed somewhat enlarged to percussion, but both these findings were inconstant. Examination of the other systems was entirely negative. The temperature for the first six hours ranged around 100° and then rose steadily until it reached 105° at the time of his death, thirteen hours following admission. The pulse was of fair quality, but progressively more rapid until it reached 150 a minute.

The general impression was that of a child who was very ill and suffering from either some acute obstruction of the bile ducts or from one of the acute hæmorrhagic diseases with secondary hepatic symptoms. His history did not seem to suggest an acute hæmolytic condition, nor was the jaundice of that type. A blood transfusion of 190 c.c. of the father's blood was given, he having been proved to be a suitable (minor) donor. The child's condition seemed

to be definitely improved and the laboratory examinations of blood, stool and urine were postponed until the following morning. Five hours after the transfusion, the child's condition became rapidly more grave and the respirations, temperature and pulse all rose. There seemed to be moderate œdema of the lungs, but no other sign.

Necropsy.—Necropsy revealed an extreme degree of jaundice with every tissue deeply bile-stained. The liver was of the usual shape, but very much smaller than normal, and was estimated to weigh only 500 grams. The entire capsular surface was finely granular in appearance and of an unusually pale yellowish brown colour. The organ felt decidedly fibrosed. On cutting a gritty, fibrous sensation was imparted to the knife and the tissues had entirely lost their normal soft, pliable structure. The cut surface was of a uniform pale yellowish brown, and no liver substance, recognizable as such, remained. The uniform diffuse fibrosis could be easily seen on scraping the cut surface, there being complete obliteration of the usual lobular arrangement. The central vein areas were not visible. The cut ends of the larger bile ducts stood slightly above the surface, were empty and not bile-stained. The common bile duct was patent down into the duodenum. The spleen was slightly enlarged and moderately firm. The cut surface was smooth, glassy and deep reddish purple in colour, with the splenic corpuseles plainly visible. Petechial hæmorrhages were present over the pericardium pleura and peritoneum. All other organs and tissues presented negative findings.

Microscopic examination of various sections of the liver revealed a widespread, almost total, destruction of the parenchyma, with an irregular diffuse fibrosis and utter distortion of the lobular structure, in which were spread small islands of liver cells. No spots of acute necrosis or any sign of regeneration of liver substance could be found. There was much reduplication of the finer biliary channels.

SUMMARY

Prior to the necropsy some form of acute atrophy of the liver was suspected together with, possibly, some fulminating hæmolytic infection.

Icterus gravis characterized by rapid hepatic insufficiency includes a number of conditions:

(1) acute necrosis (yellow atrophy); (2) sub-acute atrophy; (3) phosphorus poisoning; (4) ictero-hæmorrhagic jaundice (practically always spirochætal); (5) yellow fever; (6) acute hepatitis (diffuse; as caused by streptococcus or staphylococcus infection).

Of these, acute necrosis, subacute atrophy, and syphilis seem to be the most likely to choose from. Icterus gravis is a rare disease and the age of those affected is usually from twenty to thirty, although 43 cases in the first decade have been collected. Finally, the necropsy findings differ from this, in that the liver is softer

and cuts like a collapsed lung, rather than as tough fibrous liver tissue as in our case. In the hæmolytic or familial type of jaundice the liver is normal in size, but there are great anæmia and asthenia, and no real insufficiency of the liver. Feer, in his book on Pædiatrics under the heading of "Catarrhal Jaundice", mentions that there are rare cases starting as catarrhal jaundice which advance to cholæmic symptoms and acute atrophy of the liver. All other authorities that I have been able to consult fail to give any account of this acute fulminating type of liver failure.

Clinical and Laboratory Notes

TANNIC ACID IN IMPETIGO AND ECZEMA

By P. S. TENNANT,

Kamloops, B.C.

I should like to call to the attention of the profession a drug whose value is probably not fully appreciated. I refer to tannic acid. It was the good effect of tannic acid on burns which led me to experiment with it on various types of skin lesions.

Impetigo neonatorum is the first disease I will discuss. Many physicians have had a very tragic experience with this disease. When a particularly contagious form of impetigo occurs in a maternity ward of a hospital, months and years sometimes elapse before it can be eradicated. I observed the contagion in one of our largest hospitals. Infected infants were isolated immediately any lesions were observed. The attending staff were gowned and those caring for infected babies were not allowed near the wards containing the uninfected. The staff, in addition to being gowned, washed their hands in a disinfectant solution between the handling of each baby. Wards were closed regularly, and fumigated, and yet the infection spread in spite of all precautionary measures.

Some years after this experience, while working in a small hospital, a new-born infant, under my care, developed impetigo. There were two other infants in the ward at the same time. These were removed to a different room and a special nurse delegated to care for the infected child. Two days later a second child developed a few lesions. This problem presented itself: Why is impetigo neonatorum a disease of the newborn? The logical answer to this question is that the delicate skin of a new-born infant has not the resisting powers of that of older children and adults; hence it occurred to me to toughen the skin around the lesions of impetigo to prevent its spread.

The vesicles were ruptured with a swab dipped in a 10 per cent solution of tannic acid. The area surrounding the lesion for an inch or more was also swabbed. This treatment was followed by swabbing the areas with a 2½ per cent tannic acid solution two or three times a day for two days. The results were surprising. A few scattered lesions appeared after this treatment on the first child, but these areas were, no doubt, inoculated prior to the institution of the treatment. The second child with only a few lesions had no recurrences at all. Both children had clear skins in the course of a few days. The ward was fumigated, and there were no further cases then for a period of six months. Six months later the third case developed in this hospital. Three vesicles were present when first noticed. Tannic acid controlled these, and no further lesions appeared.

Another skin lesion which presents itself more frequently is weeping eczema, and in consequence, the clinical trial of tannic acid as a therapeutic agent in its treatment in my hands, has been much more extensive. A young lady came into my office about six years ago to consult me regarding an eczema on both hands. She looked a miserable sight as she stood with her hands held away from her body and the fingers spread. Both hands and wrists were covered by a weeping surface. The different remedies, tests and diets, had been exhausted in the treatment of her case. I was not hopeful of benefiting her at all, but she was sent home with a 10 per cent solution of tannic acid to apply twice a day. I thought it possible that the skin lesion might respond to a bland ointment, if the weeping stage could be overcome. The patient returned in a week with dry hands, and very delighted indeed. She was given a bland ointment, and in a further two weeks her eczema had almost entirely disappeared. Her hands were better than they had been for the previous five years. She has had recurrences of the skin lesion, but these

have been readily controlled by the treatment. The underlying cause of the eczema was not discovered. Since this case, of six years ago, I have treated all weeping eczemas in a like manner, with uniformly good results.

Dermatitis venenata might be expected to respond to treatment by tannic acid. However, the lesions due to poison ivy, poison oak and other plants, such as primula, have responded indifferently to tannic acid in my hands.

In treating a weeping eczema, tannic acid should only be applied until the skin is dry. It may be applied in a 2½ to a 10 per cent solution. The weaker solutions are applied more frequently than the strong solution. I usually apply a 10 per cent solution at the start, to give quick relief, and then drop to a weaker solution. When the weeping surface has completely dried up the tannic acid is discontinued. It is not necessary, and probably not advisable, to carry on treatment to the tanning stage. As soon as the skin is dry, a bland ointment is applied. The ointment used by myself is taken from the McGill Hospital Pharmacopœia.

Zinci Oxidi	2 parts
Picis Carbonis	2 parts
Pulveris Amyli	16 parts
Paraffini Mollis	16 parts

Directions for preparation: Mix the zinc oxide with the tar thoroughly and allow to stand 48 hours. Then carefully add the starch and paraffin. The above precautions are necessary to avoid the setting free of irritant hydro-carbons.

In conclusion I may say that I am claiming no originality in mentioning tannic acid in the treatment of the above diseases. I do know, however, that the drug is, at least, not in general use for eczema and impetigo, and I think those who give it a trial will be gratified by their results.

AN EARLY SIGN IN TUBERCULOUS MENINGITIS

By R. W. KIRKBY,

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Some difficulty is experienced in the early recognition of tuberculous meningitis in children, which often leads to embarrassment of the admitting officer and private physician alike. The child comes back a few days later in an entirely different condition, and we wonder how we missed it. During the past thirteen years my association with a children's service in a large sanitarium has offered ample opportunity for observing a group in which one expects to meet this dreaded complication from time to time. These children are under the direct supervision of a competent nursing staff, and the slightest upset is recorded and an explanation

accordingly sought. An early sign observed in some cases is an otherwise unexplained *vomiting*. This is frequently present before any rise in pulse or temperature takes place. In such cases a little nervous irritability is frequently observed and a peculiar lustre to the conjunctivæ. This lustre, coupled with the nervous irritability, which was sometimes apparent before the gastric upset, has, in a number of cases, led to the prognostication of the onset of a meningeal complication four days before sufficient other symptoms developed to warrant the usual diagnostic lumbar puncture. I have found this very early sign of inestimable value, and trust it may be of some assistance to others. The fact that we know our patients intimately by daily contact may contribute something to eliciting it, but I feel that its value does not depend sufficiently upon this association to render it unworkable.

AN IMPROVED TEST FOR OCCULT BLOOD, ESPECIALLY IN THE URINE

In the course of a search for a new hæmoglobin colour standard, W. J. Stone and G. T. Burke found orthotolidine useful in the detection of minute quantities of blood in urinary sediments. The continued presence of red blood cells in urinary sediments has important clinical significance in that it may attract attention to glomerular inflammatory changes, which are frequently overlooked in the absence of albuminuria or other gross evidences of disturbance. They have found frequently that red cells were excreted more or less constantly in patients with evident foci of infection. They use a 1 per cent solution of orthotolidine in chemically pure methyl alcohol and one part of glacial acetic acid and two parts of commercial hydrogen dioxide. In performing the test 15 c.c. of urine are centrifuged at about 1,500 revolutions per minute for five minutes. The supernatant fluid is poured off. A portion of the sediment is prepared for microscopic examination. To the remaining sediment two drops of the orthotolidine solution is added plus two or three drops of the acid-dioxide solution. In the presence of blood cells aggregating 100 per cubic millimetre of sediment (approximately 1,350 per cubic centimetre of urine) a greenish blue colour develops, lasting about one minute. In the presence of from 300 to 500 red cells per cubic millimetre of sediment (approximately 4,000 to 6,500 cells per cubic centimetre of urine) a deeper blue colour develops, lasting about one minute. In the presence of larger numbers of red cells, aggregating 1,000 per cubic millimetre of sediment (approximately 13,000 per cubic centimetre of urine) as in hæmorrhagic Bright's disease (glomerulonephritis) a deep blue colour develops, lasting two minutes or longer.—*J. Am. M. Ass.*, 1934, 102: 1549.

Editorial

THE ACTION OF THERAPEUTIC AGENTS

WE owe to Voltaire, I think, the well-worn gibe that a doctor is a man who puts drugs about which he knows little into a body about which he knows less. No doubt, in Voltaire's day the thrust was fully justified, as it would have been also one hundred years earlier, though not more so, when Molière so mercilessly pilloried the medical profession for its futility and vanity, or, indeed, at any time during the Middle Ages, for during this lengthy period scientific therapeutics cannot be said to have made any particular progress. One might have expected something better, however, for the pioneer work in research physiology, the *De Motu Cordis*, had appeared two generations before Voltaire was born. Why the child of Harvey was forgotten or ignored for so long is beside our purpose to enquire here, but there were several reasons for it. It was, clearly, premature. The empiricism and polypharmacy that prevailed until comparatively recent times brought its inevitable sequel in a distrust of all drugs, and by the latter part of the nineteenth century a sort of therapeutic nihilism was rampant. However, with the discovery of hormones and vitamins this attitude has been changed, and we, of the twentieth century, are prepared to believe that the functions of the body, whether in health or disease, can be influenced by chemical agents. These agents may be, and often are, introduced from without as drugs or foodstuffs, but the later viewpoint is strengthened by the fact that it has been fully demonstrated that the body can manufacture its own chemical substances, which are potent forces in controlling growth and development, and, moreover, can be utilized for the correction of pathological states. We owe this change of attitude to the intensive studies of the present-day physiologists and pharmacologists, who have achieved results that are simply astounding in their character and implications and are full of promise. We may pause with profit to learn something of what has been accomplished in the realm of scientific therapeutics,

and, incidentally, perhaps, discover how far our craft is fair game for the missiles of our modern Voltaires.

Drugs and other remedial substances are, of course, used in medicine for the cure of disease and the prolongation of life. We have used them in the past, and still use them symptomatically for the relief of pain, for insomnia, and other distress, for example, but we may truthfully say that our chief aim nowadays is to discover the normal processes of the body, so that when they are deranged we may, through our remedial agents, be able to guide them in the proper direction. We may at times use drugs to combat symptoms, but, nevertheless, we recognize the *vis medicatrix Naturæ*. We seek to understand Nature and to assist her. This is the scientific attitude. But while we do this we probably, most of us, have only a vague idea as to how our remedies produce their effects.

We used to be taught that drugs had a selective action on various organs, even on parts of organs, and on tissues. Thus some picked out the heart, some the central nervous system, some the terminations of the motor nerves in muscle, some the secreting cells of the kidney, and so on. Their effects might be brought about by direct action on the cells or nerves of supply. Drugs which increased the activity of any organ or function were said to stimulate it; those which lessened the activity were said to depress it. All this seemed simple, but actually was very crude. One would conclude that the distribution of a drug in the various organs and tissues of the body must influence its action, and this is doubtless so, but it does not necessarily follow that the organ which contains the greatest amount will show the greatest effects. Examples might be cited to prove this. Much seems to depend on the character of the drug and that of the cells comprising the organ, and on the relations between the cells and the fluid that bathes them.

Leaving out of account the relatively few

cases in which a drug acts in a physical or chemical way by simple contact, as, for example, when bicarbonate of soda is used to neutralize the acid in the gastric juice, it has been widely held that when a drug affects a cell it enters into a definite chemical combination with its substance, similarly to the reactions met with in a chemical laboratory. There are difficulties in accepting this view. One of these is that the same action may be induced by a series of drugs which have no chemical reactions in common, and, therefore, cannot be thought to enter into the same chemical combination with the cell protoplasm. Consequently, some would attribute the action of drugs rather to their physical properties. If a drug is not soluble in the fluids of the body it cannot be absorbed by the blood, and, if it is not soluble in the contents of the cell it cannot readily enter the cell. On this assumption it has been held that many effects of drugs are to be attributed to selective absorption alone, a drug acting on all cells into which it can enter by disturbing the relations of the cell constituents in which it is dissolved. Cogent objections have also been raised to this idea. The possibility that some effects of drugs are due to alterations produced in the surface tension of cells in relation to the fluids that bathe them, associated sometimes with a change of electrical charge, has been suggested. While, in the main, it may be admitted that drugs act on cells only when they have penetrated into the interior, yet instances are known where the effects of drugs must be attributed to their failure to enter the cells. Finally, it has been suggested that drugs produce their effects by altering the electrical charges of the intracellular membranes, thus retarding or accelerating the passage of ions through them. There is, doubtless, an amount of truth in all of these views, but it is quite certain that the activity of drugs is dependent on a considerable number and variety of factors, and that pharmacological action is not so simple that it can be brought under one law. Much more work is required before these factors can be given their proper weight. However, there are certain lines of thought on which we can report distinct progress. In particular, these have a bearing on the question of nervous stimulation, and on the action of

hormones and vitamins. We have in mind here the researches of such men as Langley, Elliott, Dixon, Dale, Loewi, Cannon and Meyers.

To Langley we owe the observation, now well attested, that the effect of adrenaline on any part of the body is the same as if the sympathetic nerves going to that part were stimulated. In other words, a chemical substance can imitate a nervous one. Further, adrenaline produces no effect on a structure that has never possessed a sympathetic innervation, but Elliott found that, once a structure has possessed it, cutting of the sympathetic innervation does not abolish the effects of adrenaline upon it; indeed, the effects are increased. Langley and Elliott, therefore, independently, advanced the idea that there is a receptive, sometimes called an intermediary, substance beyond the nerve ending on which the drug acts. Similarly, W. E. Dixon, of Cambridge, showed in 1907 that after stimulating the vagus nerve a substance could be extracted from the heart muscle which could inhibit other heart muscle and could be antagonized by atropine, exactly as atropine antagonizes vagus stimulation. It was shown later by Dale and by Loewi (1921) that the substance produced was acetylcholine, and that it was discharged not only when the vagus to the heart was stimulated but also whenever any parasympathetic nerves came into action. Physostigmine, also, imitates the effect of stimulation of the parasympathetic. According to Loewi, this is because physostigmine prevents the blood or the tissues from destroying the acetylcholine produced. It should be noted that if atropine be given and the vagus be subsequently stimulated just as much acetylcholine is produced as before, but the atropine prevents it from uniting with the receptive substance. Again, Cannon has shown that stimulation of the sympathetic produces an adrenaline-like substance in other structures besides the adrenal medulla. From all this Langdon Brown¹ deduces a general rule, that nervous stimuli may liberate chemical substances which transform a nervous stimulus into a chemical reaction. Or otherwise, as Hopkins puts it, "substances produced temporarily and

1. BROWN, W. L.: How do drugs act? *Brit. M. J.*, 1933, 2: 1007.

locally, by virtue of their chemical properties, translate for the tissues the messages of the nerves".

If a drug may seize upon the receptive substance so may a toxin. Some illuminating work in this direction has been done by G. N. Meyers,² of Cambridge. He showed that a therapeutic drug may fasten on the receptive substance and so prevent the ingress of a toxin. Thus, if digitalis were given first the toxin of diphtheria could be prevented from attacking the heart. This is a most important observation. There has for long been a difference of opinion over the question whether digitalis exerts any beneficial action in a febrile (and presumably toxic) condition. One would feel, in the light of this work, that digitalis, given prophylactically, would be entirely efficacious in protecting the heart; if given during the fever, but still early, it could be expected to do good by preventing the toxin from swamp- ing the heart.

From the endocrine system we can get an illustration of how drugs (we may include hormones with drugs) can antagonize one another. Pituitrin and insulin are antagonistic, but this antagonism is not chemical but, rather, physiological. The vasopressin element of pituitrin empties the liver of its stores of glycogen, while insulin stores up glucose in the liver in the form of glycogen. Again, drugs may act by increasing or diminishing the activity of a hormone. Thus, in Graves' disease the sympathetic system is over-active. Thyroxine stimulates the sympathetic and exaggerates the response. Quinine hydrobromide depresses the sympathetic, and the more thyroxine produced, the more difficult it is to produce cinchonism.

In the domain of vitamins many interesting problems have been worked out, and others are under investigation. Lack of space precludes the marshalling of the evidence, but it would appear that in some cases drugs are capable of activating vitamins. Thus, the subacute combined degeneration of the spinal cord that is sometimes met with in pernicious anæmia has been attributed to a lack of vitamin A. Apparently the body in

this case has lost the power of utilizing vitamin A, and feeding it with this vitamin is of little or no avail, but results are obtained if at the same time massive doses of iron are exhibited.

Vaccines and drugs apparently act by exciting the formation of a new, protective, substance in the body. Emetine in dysentery and salvarsan in syphilis are ineffective against their respective parasites *in vitro*, but injected into the body are potent. In such cases we infer that the specific effect produced is due to a chemical interaction between the drug and some constituent of the cell.

Attempts have been made to associate physiological action with chemical or physical constitution, not always with success. Some of the hypnotics differ widely in chemical constitution, but possess in common the property of solubility in fats and lipoids. They tend, therefore, to accumulate where such substances abound, as in the central nervous system. Recently, Cook, Dodds and Hewett³ have demonstrated in a striking way an instance of relation between physiological action and chemical structure. This is well summarized in the words of Prof. Langdon Brown (*loc. cit.*). "Œstrin, the ovarian hormone; calciferol, which has such an influence on the orderly growth of bone; and the carcinogenic substances to be found in tar, all contain the condensed carbon rings which we call anthracene. Thus it appears that normal reproductive activity, normal growth of bone, and that irregular, disorderly, unrestrained growth which constitutes malignancy are alike conditioned by this condensed ring, chemical alterations in it, apparently merely of hydrogenation, leading to extraordinarily different types of growth. The whole subject assumes fresh interest when we recall that anthracene is normally a coal-tar derivative, and was therefore formed under the influence of sunlight ages ago, just as calciferol has been formed in our own subcutaneous tissues by the bright sunlight of this summer."

A.G.N.

2. MYERS, G. N.: Experimental investigation on the treatment of toxæmia, *J. Pharmacol. and Exper. Therap.*, 1933, **49**: 483.

3. COOK, J. W., DODDS, E. C. and HEWETT, C. L.: Synthetic oestrus-exciting compound, *Nature*, 1933, **131**: 56. See also, COOK, J. W. and DODDS, E. C.: Sex-hormones and cancer-producing compounds, *Nature*, 1933, **131**: 205.

DIVINYL OXIDE AND CYCLOPROPANE, THE NEW ANÆSTHETICS
OF CHOICE IN OBSTETRIC PRACTICE

NOWADAYS much is being written about the necessity of making what should be a normal function, pregnancy and parturition, safe for the proletariat. Insistence is being laid, rightly, on pre-natal care, the restriction of operative procedures to the irreducible minimum, and on the protection of the prospective mother from infection. All this is to the good, of course, and will conduce to the end that all are hoping for, a reduction in the maternal and neo-natal death rates. Less, however, is being heard about the subject of anæsthesia in child-birth, and yet the choice of the anæsthetic here is far from unimportant. In some cases, even if it be admitted that they are but few, the character of the anæsthetic employed may tilt the scale from life to death. The employment of the most suitable anæsthetic and its proper administration cannot fail to increase the comfort and safety of the mother during the ordeal itself, and necessarily must add to the assurance of the accoucheur, particularly when manipulations and operations are required; and a capable and confident accoucheur, who is willing to utilize the best that science has to offer, who understands anæsthetics, and, accordingly, has the situation well in hand, spells safety and life.

Certain qualities are highly desirable, if not indeed absolutely essential, in an anæsthetic which shall be ideal for obstetric work. These are that anæsthesia must be quickly and agreeably induced, satisfactorily maintained at any desired depth with ready flexibility, and recovered from easily and uneventfully; moreover, it must work no harm to mother or child. Not many anæsthetics measure up to these requirements. In the past, and, in general, even now, the anæsthetics most employed in obstetric work are chloroform, ether and nitrous oxide. We leave out of account, designedly, the adjuvants, morphine, scopolamine and heroin. In spite of the fact that men of wide experience still hold that chloroform is safe when rightly administered, many of us can recall cases where its use seemed to have pushed the patient over the edge, notably from acute degeneration of the liver, and think that it might well be replaced by some

anæsthetic safer for general use. Nor should its depressing action on the heart be forgotten. Ether has the disadvantage of being unpleasant to take, causes irritation of the respiratory apparatus, is excitant for some, stimulates an undesirable flow of mucus, leads to cyanosis, and has troublesome sequelæ when being eliminated. Gas-oxygen is good, but its administration, requiring an expensive and somewhat bulky apparatus, is practically limited to hospital work. What is needed is an anæsthetic conforming to the ideals mentioned above, one which is cheap, and can be administered in the home. Such is not easy to find.

Much intensive work has been done within the last two or three years to discover the ideal anæsthetic and, undoubtedly, progress has been made. Not only have new anæsthetics been produced but their actions have been carefully studied. The danger is that when so many are before him the practitioner may feel confused and be content to worry along in the old way. We feel, however, that the whole subject will repay investigation. We should be ready, even anxious, to improve.

Dr. Wesley Bourne, of Montreal, has been active in the study of some of these newer anæsthetics, and his recent papers on the subject are commended to the attention of all. In his opinion divinyl oxide and cyclopropane come close to the standards that are here set up for the ideal anæsthetic for obstetric work. In the first of his articles that we shall notice¹ a careful study is presented of 50 parturient women to whom divinyl oxide was administered at the Royal Victoria Montreal Maternity Hospital*. We believe this to be the first occasion on which this anæsthetic has been administered in obstetric cases. The technique of administration was that of bubbling oxygen through divinyl oxide at the rate of about 700 c.c. per minute in a closed system, with a carbon dioxide absorption attachment (Foregger).

1. BOURNE, W.: Divinyl oxide anæsthesia in obstetrics. *The Lancet*, 1934, 1: 566.

*At the date of writing Doctor Bourne has notes of 222 cases in which divinyl oxide has been administered. He is confirmed in his opinions as a result.

This method precludes asphyxia and waste of material. Divinyl oxide may also be dropped on a small "open" mask in the way in which chloroform is usually administered. The 34 women to whom a mixture of divinyl oxide and oxygen was given were treated as follows. There were 29 spontaneous deliveries, in 25 of which episiotomy was performed; 3 mid-forceps cases; 1 bag induction; and 1 Cæsarean section with sterilization. The 14 patients who received divinyl oxide alone were classified as 10 spontaneous deliveries, in which there were 7 episiotomies; 2 mid-forceps; and 2 low-forceps cases. On patients who were anæsthetized with a mixture of nitrous oxide, oxygen and divinyl oxide 1 high-forceps and 1 Cæsarean operation were performed. Doctor Bourne remarks that the rapidity with which anæsthesia is induced is very striking, a few inhalations being sufficient. There is very little excitement, any desired degree of muscular relaxation can be obtained, and recovery is very rapid. In its effects on respiration and circulation divinyl oxide compares favourably with ether (diethyl oxide). Post-anæsthetic nausea and vomiting are no more frequent than is usual in obstetrics. Using the bromsulphalein dye test for liver function, Doctor Bourne finds that the administration of divinyl oxide under the circumstances mentioned is followed by very slight retention of the dye, and consequently, he infers that there is practically no damage to the liver. He concludes, "It would seem that divinyl oxide is a very suitable anæsthetic for employment in obstetrics. It permits of rapid application, equally rapid recovery, and a satisfactory maintenance of any degree of narcosis with minimal danger to the mother and child. Although it is preferable that this anæsthetic be administered with oxygen, yet it may be given with relative safety by itself."

In a second paper² Doctor Bourne gives his experiences with cyclopropane in a series of 34 parturient women at the Royal Victoria Montreal Maternity Hospital. Henderson and Lucas, of Toronto, were the discoverers of the anæsthetic properties of cyclopropane, and, from a careful study of its effects on

circulation and respiration and its influence on metabolism, felt justified in suggesting it as a safe anæsthetic for man³. Following up this idea, Stiles, Neff, Rovenstine and Waters⁴, of the University of Wisconsin, employed cyclopropane as an anæsthetic during surgical operations. These observers found that cyclopropane was equally as efficient as other gaseous anæsthetics, and in much lower concentrations; that an excess of oxygen may be administered with this potent anæsthetic; that surgical anæsthesia can be obtained in from three to five minutes; that it causes relaxation comparable with that produced by ether; that the blood pressure, pulse and respiratory rates are not altered to any appreciable extent; that recovery takes place in less than five minutes; and that the after-effects are very slight. In view of this favourable report Doctor Bourne felt it safe to employ this anæsthetic in obstetric work. Satisfactory analgesia was easily produced when very small quantities of cyclopropane were inhaled with oxygen. He thinks it would be quite safe to relieve the pains of labour with cyclopropane much earlier than has been done, inasmuch as this agent does not inhibit the uterine contractions and so much oxygen can be used. From experimental work done in the Department of Pharmacology of McGill University, and from his clinical studies, Doctor Bourne does not find that cyclopropane works any damage to the liver. He gives the following five reasons why he regards cyclopropane as a very suitable anæsthetic for the relief of the pains of labour: (1) an abundance of oxygen is given with the cyclopropane; (2) circulation and respiration are not depressed; (3) anæsthesia is produced without appreciable metabolic disturbance; (4) liver function is not impaired; and (5) anæsthesia is quickly and agreeably induced, satisfactorily maintained at any desired depth with ready flexibility and with minimal danger to the mother and child, and recovered from easily and uneventfully.

2. BOURNE, W.: Cyclopropane anæsthesia in obstetrics, *The Lancet*, 1934, 2: 20.

3. HENDERSON, V. E. and LUCAS, G. H. W.: Cyclopropane: a new anæsthetic. *Current Researches in Anæsth. and Analg.*, 1930, 9: 1.

4. STILES, J. A., NEFF, W. B., ROVENSTINE, E. A. and WATERS, R. M.: Cyclopropane as an anæsthetic agent: a preliminary clinical report., *ibid.*, 1934, 13: 56.

Comparing divinyl oxide and cyclopropane from a pharmacological standpoint, it may be said that they are very similar in their effects and freedom from objectionable qualities. Both are inflammable, but not more so than ether-oxygen. Divinyl oxide has a slightly objectionable odour, but cyclopropane is more pleasant. Any objections on this score can be largely overcome by using the closed method of administration. Divinyl oxide and cyclopropane are both preferable to nitrous oxide, as a larger

proportion of oxygen can be used. Both are expensive, but, doubtless, this disadvantage will be overcome in time. The use of the closed method of administration will, of course, reduce waste to a minimum. Cyclopropane, like divinyl oxide, can be given by some apparatus like the Foregger. On the whole, cyclopropane is more adapted for use in institutions, while divinyl oxide is more suited to the needs of the general practitioner.

A.G.N.

Editorial Comments

Amendments to the Food and Drugs Act

We are indebted to Dr. J. J. Heagerty, Chief Executive Assistant, Department of Pensions and National Health, Ottawa, for a copy of Bill 70, An Act to Amend the Food and Drugs Act, which was passed at the last session of the Federal Parliament and comes into force on January 1, 1935. It had been found that there was a discrepancy between the provisions of the Food and Drugs Act and those of the Proprietary or Patent Medicine Act which rendered the latter nugatory in a certain important direction. Under the Proprietary or Patent Medicine Act remedies are not permitted to be sold for the diseases listed in Schedule A, whereas they might be sold under the Food and Drugs Act. One of the main purposes of the amending Act was to insert Schedule A of the Proprietary or Patent Medicine Act in the Food and Drugs Act, thereby bringing both Acts into conformity. Schedule A at present lists the following: alcoholism, appendicitis, arteriosclerosis, blood poisoning, Bright's disease, cancer, diabetes, diphtheria, dropsy, epilepsy, erysipelas, gall stones, kidney stones, bladder stones, gangrene, gastric and duodenal ulcers, goitre, heart diseases, high blood pressure, infantile paralysis, influenza, lockjaw, locomotor ataxia, obesity, pleurisy, pneumonia, ruptures, scarlet fever, sexual impotence, smallpox, spinal meningitis, trachoma, tuberculosis, tumours, typhoid fever, and venereal diseases. It will be generally agreed that a great step forward has been taken when legislation has now been enacted which will make illegal the sale and advertising of nostrums for the treatment of such an important array of diseases and abnormal conditions. Medical men know, if the generality of the public do not, that recourse to self-treatment with so-called remedies is often injurious, and, indeed, may prove fatal, especially when dealing with certain diseases, notably, diphtheria and cancer. "Delays are dangerous", here as elsewhere. No loophole now exists through which unscrupulous vendors can

slip by the provisions of the Proprietary or Patent Medicine Act, and this is all to the good. Section 6A of the amended Food and Drugs Act reads: "No person or company shall import, offer for sale or sell any remedy represented by label or by advertisement to the general public as a treatment for any of the diseases, disorders, or abnormal physical states named or included in Schedule A to this Act or in any amendment to such Schedule."

In the original Food and Drugs Act Schedule B appears as "Schedule", simply. The omission of the letter "B" was due to an error and is now corrected. Schedule B is a list of vegetable preparations, animal tissues, viruses, toxins, vaccines, and compounds of arsenic, all of which are subject to biological testing as to potency and toxicity.

It is important to note that the Governor-in-Council is granted authority to add to or take from Schedules A and B. This makes provision for changing conditions which may possibly arise from increased knowledge of the class of preparations listed therein, and creates much leeway.

We gladly agree that the effect of this recent legislation is to tighten the clamps on undesirable advertising and to protect the public from the wiles of unscrupulous vendors of proprietary remedies. In the Proprietary or Patent Medicine Act we, in Canada, have an Act that is more effective for its purpose than most. We could wish, however, that legislation might go still farther. We have already in these columns called attention to the dangers accruing from the excessive and uncontrolled use of certain drugs, such as barbituric acid derivatives, amidopyrine, and dinitrophenol. We deprecate the sale of these "over the counter" and without a physician's prescription, and hope for the time when legislation will also take care of this menace. The use of such drugs as veronal, luminal, and dial, is widespread among the laity and appears to be increasing. Some toilet

articles, also, need scrutiny. The situation certainly calls for regulation. We note with satisfaction that Obesity is one of the conditions listed in Schedule A, for which a remedy may not be advertised or sold. Dinitrophenol, perhaps the most dangerous of the drugs cited above, which, at the moment, has its only *raison d'être* in the process of "slimming", would appear to be barred under this regulation.

The wide scope and applicability, and, inferentially, the great value, of the two Acts above referred to may be gathered from the following figures kindly supplied by Dr. Heagerty.

Deaths in Canada during the year 1932 from diseases mentioned in Schedule "A" were as follows: alcoholism, 136; appendicitis, 1,454; arteriosclerosis (diseases of the arteries), 6,798; blood poisoning (purulent infection, septicæmia), 212; cancer, 10,024; diabetes, 1,343; diphtheria, 398; epilepsy, 319; erysipelas, 229; gastric and duodenal ulcers (diseases of the stomach), 1,349; goitre (diseases of the thyroid and parathyroid), 350; heart diseases, 15,328; infantile paralysis, 164; influenza, 4,236; locomotor ataxia, 66; pleurisy, 366; pneumonia, 7,045; ruptures (hernia, intestinal obstruction), 947; scarlet fever, 197; smallpox, 17; spinal meningitis, 139; tuberculosis, 7,166; tumours, 637; typhoid fever, 339; venereal disease (syphilis), 514; total, 59,773.

A.G.N.

The Canadian Red Cross Society

The Annual Report of the Canadian Red Cross Society for 1933 is before us and is a stimulating and encouraging document. It well merits perusal from beginning to end. We gladly endeavour to give currency to some, at least, of the activities of this most meritorious Society.

We note, first, that despite four years of the most serious economic difficulties the Canadian Red Cross Society has been able to maintain its usual activities and even embark on new undertakings. Nowhere has there been any essential reduction in its program. The total revenue for the year amounted to almost \$1,120,000, an increase of about \$150,000. Of this sum general contributions amounted to slightly over \$410,000, a reduction of almost \$100,000 from the previous year's figures, but in view of the fact that the total for 1932 included the \$122,000 subscribed to the National Emergency Fund, the actual situation is that the ordinary general contributions for Red Cross work in 1933 exceeded those of any previous year since the peace-time program was undertaken. This means that the ordinary general contributions were increased by about 5 per cent. As the Report states, this speaks volumes for the general estimation in

which the Red Cross in Canada is held. During 1933 the Red Cross disbursed no less than \$1,200,000. Through the institution of drastic economies it was possible to carry on not only the many already established forms of Red Cross service but to provide substantial assistance in the various forms of relief work that have become necessitated for various reasons throughout Canada. The Report points out, however, that in the past few years there has been a continued depletion of reserves. This, of course, cannot go on indefinitely, and the time has come when the year's work must be financed from the year's revenues. It is estimated that "with gross revenues of some \$650,000 the Red Cross will be able to continue to provide for the needs of disabled ex-service men and their dependents, strengthen the organization of the Junior Red Cross, extend its Outpost Hospital Service, increase the number of Home Nursing Classes and Visiting Housekeepers, broaden the field of its health work, and undertake further measures for 'the improvement of health, the prevention of disease, and the mitigation of suffering'." Some other statistics are of interest. Nursing care was given by Red Cross Outpost Nurses, to 24,205 persons, an increase over the previous year of 1,424. The number of crippled children cared for was 1,126, an increase of 148. There were 1,436 confinement cases, an increase of 50. In a series of 710 cases there were only 2 maternal deaths, a rate of 2.8 per thousand, a very good figure, considering the tremendous handicaps under which the Red Cross nurses care for many of these patients. If the number of school children inspected be included, it is seen that the nurses gave attention of one kind or another to 38,922 persons. Relief work took many forms. We note that under Red Cross auspices a quarter of a million nights' lodgings were furnished, at least half a million garments were distributed, and almost a million and a half meals were served. We quote again from the Report. "Assistance to ex-soldiers has taken a bewildering variety of forms. Besides the inescapable and universal three-fold need for food, clothing and shelter, the Red Cross has been called upon to meet almost every known human want. The Society has helped soldiers and their families in sickness, has provided diabetics with insulin, under-nourished children with cod liver oil and over 100,000 quarts of milk, and invalids with comforts. It has paid transportation for dozens of stranded men, either to their homes or to places where they could get work; it has furnished dental service, artificial limbs, glasses, and a score of similar necessities, and, indeed, has supplied all manner of things necessary for comfort and welfare." This recital speaks for itself. Nothing more is needed. The

Canadian Red Cross Society is heartily commended to the sympathies and support of all our readers.

A.G.N.

The Annual Meeting of the British Medical Association at Melbourne, Australia

The next Annual Meeting of the British Medical Association will be held at Melbourne during the week of September 9, 1935. This is the first occasion on which the Association will have convened in Australia. Naturally, the Council is extremely anxious that the number attending shall be as large as possible. As our Canadian Association is in affiliation with the British Medical Association it is hoped that a worthy representation of the Canadian profession may find it possible to be present. In order to save time and add to the interest of the occasion a number of special trips have been arranged which will enable those participating to visit many remarkable places. Naturally, these itineraries have been arranged to start from England, but it will, doubtless, be possible for Canadians to pick up the party at convenient points in Canada and the United States. In view of the fact that a considerable portion of the British contingent will arrive in New York on the fourth of August it had been hoped that the conjoint Annual Meeting of the Canadian and American Medical Associations, which is slated for Atlantic City in 1935, could have been arranged to take place about that date, in order to allow of our overseas colleagues

being present, but this was not found to be feasible.

Two itineraries will appeal to Canadians. Number 1 leaves New York on August 5th and calls at Washington, Chicago, Albuquerque, Grand Canyon, Los Angeles, San Francisco, Honolulu, Suva, Auckland, N.Z., Sydney, and Melbourne. Number 2 leaves Montreal on August 3rd and calls at Toronto, Niagara Falls, the Great Lakes, Sault Ste. Marie, Fort William, Banff, Lake Louise, Vancouver, and San Francisco. The rest of the trip will be as in Itinerary Number One.

All arrangements for the journey are in the hands of the Financial Secretary and Business Manager of the British Medical Association, British Medical Association House, London, who are associated with Messrs. Pickfords Travel Service, 205 High Holborn, London, W.C.1.

We are asked to announce that the Victorian Medical Women's Society extends a cordial invitation to Canadian medical women to attend the Meeting in Melbourne and is prepared to offer them hospitality. Any Canadian medical women who would like to take advantage of this opportunity are invited to communicate with Dr. Brenda B. Scott, 250 High St., Malvern, Melbourne, Victoria, Australia.

There can be no doubt that this meeting in Melbourne will prove of extraordinary interest. Our Association is to delegate official representatives and it will be fitting if they can be supported by a considerable and worthy representation of our members. The Annual Meeting in Australia is cordially commended to our readers.

A.G.N.

Retrospect

THE SEX-HORMONES*

BY G. F. MARRIAN,
*Department of Biochemistry,
University of Toronto,
Toronto*

THE ŒSTRUS-PRODUCING HORMONE

The effect of ovariectomy on experimental animals has been well known for many years. Ovariectomy is followed by the disappearance of the cyclic symptoms of Œstrus and the accompanying changes in the accessory sexual organs. The accessory sexual organs in fact undergo a rapid and severe degeneration after the operation. It was clear therefore that the growth and activity of the accessory sex organs was controlled by the ovary. Some of the earlier workers suggested that this influence of the

ovary was essentially a nervous one. That this could not be the case was shown by experiments with ovarian grafts. Ribbert (1898), Krauer (1910), Marshall and Jolly, and many others showed that if the ovaries were removed from a female animal and grafted into another site in the body—usually the peritoneum—the Œstrous cycle continued and no degenerative changes appeared in the accessory sex organs, provided that the graft established vascular connections. These experiments indicated that the ovary exerted its influence on the accessory organs through a chemical substance which it elaborated and poured into the blood. Further evidence supporting this view was obtained by other ingenious grafting experiments by Ribbert, in 1898, and by Loeb (1908). These workers grafted portions of various accessory organs to other sites in the body, leaving the ovaries intact. In both experiments the grafted accessory tissues showed the same changes at the Œstrous period as they would have done in their normal sites.

* Paper read before the Section of Obstetrics and Gynaecology, Academy of Medicine, Toronto, October 5, 1933.

The general realization that the development of, and changes in, the accessory organs were controlled by an ovarian hormone naturally led to many attempts to prepare ovarian extracts which, on administration to ovariectomized or oestrous animals, would cause the typical oestrous changes in the accessory sex organs. For several years these attempts ended in failure, but in 1906 Marshall and Jolly injected a saline extract of ovarian tissue into an oestrous bitch and obtained transient oestrous symptoms. The extract of Marshall and Jolly was not particularly potent, and it was not until 1912 that a method of preparing ovarian extract was elaborated that yielded products with a high activity. Iscovesco (1912) and Fellner in the same year found that if fat-solvents, such as alcohol and ether, were used to extract the ovaries instead of water or saline highly potent extracts could be obtained. Thus it was clearly established that the hormone had distinct fat-like solubilities.

Now at this time it was impossible to assay the potency of an extract accurately. The usual method of determining whether or not an extract was active was to inject some into an ovariectomized or a young virgin rabbit, to kill the rabbit, and then to determine whether the changes characteristic of normal oestrus had been produced in the uterus. It is obvious that such a procedure could not readily be made the basis for a quantitative method of assay. Without any accurate method little progress could be made in the work of purifying the crude extracts.

This difficulty was overcome in 1923 by Allen and Doisy. Previously to this, Stockard and Papinicolaou had shown, in 1917, that the different stages in the oestrous cycle of the guinea pig were characterized by well defined changes in the cell contents of the vagina. Evans in 1922 and Allen in the same year showed that similar vaginal changes characterized the different stages in the oestrous cycles of the rat and mouse. During the dioestrus, or resting, stage the cell contents of the vagina were found to consist mainly of leucocytes together with a few nucleated epithelial cells. During the period of active growth in the uterus and vagina (at pro-oestrus), the leucocytes disappeared entirely and only nucleated epithelial cells were found. At the height of oestrus the epithelial cells of the vaginal mucosa became cornified and sloughed off in large numbers. Thus it was possible, by examining microscopically the vaginal smear of a rat or mouse, to determine exactly at what stage of the oestrous cycle it was. An ovariectomized mouse has the same type of vaginal smear as is seen in dioestrus in the normal animal. Allen and Doisy found that if an ovarian extract was injected into an ovariectomized mouse or rat about 48 hours later a vaginal smear of the typical oestrous type appeared. This reaction was clearly ideal as the

basis for a quantitative method of assay. By using a large number of rats or mice they were able to determine the smallest amount of extract necessary to produce this vaginal cornification; this amount they defined as the rat or mouse unit.

Later work has shown that in order that a given dose of oestrin can exert its full effect on an animal a certain concentration of the hormone must be kept up in the blood for a period of about 36 hours. From this it follows that the apparent potency of a preparation administered by subcutaneous injections will largely depend upon its rate of absorption into the blood. Generally speaking, slow absorption will tend to increase the intensity of the physiological action. If a single injection of a fairly pure preparation in a thin aqueous suspension is administered it will be rapidly absorbed, and it will not be able to exert its full physiological effect. The physiological effect can be increased in two ways, either by giving a series of small injections instead of one large one, or by injecting an oil solution to delay absorption.

Two facts of considerable practical importance depend upon this. The actual value of a rat or mouse unit is affected to a considerable extent by the actual technique of assay. The term rat or mouse unit has therefore little meaning to anyone not acquainted with the method of assay employed. The recent introduction of an International Unit for oestrin, based on the activity of a certain weight of a pure preparation, will obviously be of very great value.

The second important point is in connection with the activity by mouth. Earlier workers claimed that oestrin was inactive when given by mouth. It was then found that it was active, but only when given in doses of 20 to 100 times that of the subcutaneous dose. It was then realized that this low oral activity was not due to destruction in the digestive tract but was merely a question of the rate of absorption into the blood. By administering the hormone by mouth in a suitable medium it was found possible to increase its activity to about one-quarter of that by the subcutaneous route. Schoeller and his co-workers found that the activity by mouth was increased when the hormone was dissolved in dilute alcohol.

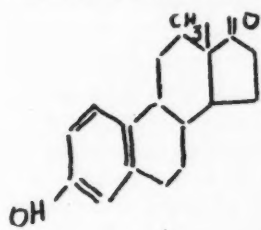
There is no doubt that in the future, when large supplies of the hormone are available at a low price, oral administration will be extensively used in clinical work. At the present time, however, there are two serious objections. Since the full physiological effect of a given amount of oestrin is not obtained by oral administration, this method is wasteful of expensive material; further, since the physiological potency of orally administered oestrin depends upon the rate of absorption from the digestive tract, the potency will necessarily depend to some extent on the nature of the contents of the digestive tract. The results obtained from oral administration

must therefore be less uniform and reproducible than those obtained by subcutaneous administration. At the present time, when the clinical use of œstrin is in the experimental stage, subcutaneous administration would seem to be preferable.

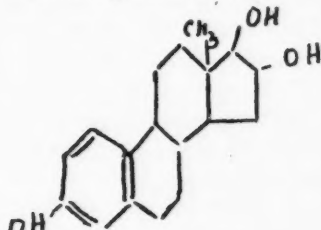
A few years ago, Parkes and I found that the amount of œstrin necessary to produce the full œstrous changes in the uterus of an ovariectomized mouse was 200 times the amount necessary to cause vaginal cornification. We also found that 200 of the so-called mouse units were necessary to get an ovariectomized mouse to copulate. That is to say the mouse unit is only 1/200th of the amount of œstrin required to produce full œstrus. In the light of this finding, some of the early clinical trials of œstrin where only a few 100 mouse or rat units were injected looked ludicrous, and it is not surprising that they yielded disappointing results. Calculating on a body weight basis, which was a justifiable procedure, Parkes and I estimated that the effective physiological dose of œstrin for an ovariectomized woman would be about 250,000 of our mouse units. It is not to be expected that in the attempted treatment of amenorrhœa such large doses would be necessary, but our results serve to show that larger doses than have in the past been administered might be advisable.

The recent great advances in chemical work on œstrin were made possible by the important discovery of Zondek and Ascheim in 1927 that the urine of pregnant women contained large amounts of the hormone. This discovery provided a cheap and easily obtainable starting material for chemical investigation. Shortly afterwards Zondek showed that the urine of pregnant mares was even a richer source of the hormone. Within two years of this discovery, the isolation of œstrus-producing substances in a state of chemical purity was reported independently, and almost simultaneously, from four different laboratories. Two chemically distinct but closely related substances were isolated from human urine, while more recently Girard has shown that mare's urine contains three more different œstrogenic substances.

Recent work from several laboratories makes it almost certain that the two substances in human urine have the following structures:



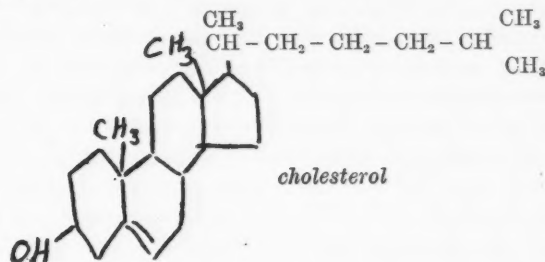
Theelin (Doisy)
Ketohydroxyœstrin (Marrian)
œSTRONE (name accepted by all
interested workers in England)



Theelol
Trihydroxyœstrin
œSTRIOL

The three substances isolated from mare's urine by Girard differ from œstrone by being more unsaturated.

The relationship between the œstrins and the sterols and bile acids will be clear from the following formula which is now believed to represent cholesterol.



It is considered to be probable that the œstrins arise in the body from the degradation of cholesterol or one of the bile acids.

The greater part of the œstrin present in urine is in a form in which it cannot be extracted by ether. In order to obtain maximum yields by ether extraction a preliminary boiling of the urine with acid is necessary. Boiling with alkali is ineffective. This fact strongly suggests that most of the œstrin in the urine is combined with some acid to form an ether-insoluble, water-soluble ester. Since this œstrin ester can be hydrolysed by acid and not by alkali, and since it is well known that many phenolic substances are excreted in combination with sulphuric acid, it seems possible that this so-far unidentified œstrin ester is a sulphate.

The water-soluble, ether-insoluble, œstrogenic substance (emmenin), which has been detected in the placenta by Collip, and which in acid hydrolysis yields œstriol, is probably a similar type of ester. It seems unlikely that emmenin can have, qualitatively, a different physiological action to œstriol, although, quantitatively, its action may be expected to be different owing to its different rate of absorption into the blood. A decision on this point cannot however be arrived at until emmenin is isolated in a chemically pure form.

At this point reference may be made to the value of chemical work in hormones to the physiologist and to the clinician. Much of the work on the physiological action of œstrin was done at a time when only extremely impure preparations were available. Repetition of this work on the chemically pure hormone is revealing that certain of the effects hitherto ascribed to œstrin are due merely to the action of impurities associated with it. In the present experimental state of the clinical use of œstrin it would seem advisable therefore to limit all clinical trials to the chemically pure material, so that any effects observed can definitely be said to be due to the action of the hormone itself.

ANTERIOR PITUITARY

Associated with the ovary there are three separate series of cyclic changes.

1. The periodic appearance of œstrus, due presumably to the periodic production of œstrin by the ovary.

2. The periodic growth, maturation and ovulation of the Graafian follicles. I should here point out that, contrary to what is often implied in the literature, œstrus does not necessarily depend upon ovulation. In certain animals, like the rabbit and ferret, œstrus and ovulation are quite separate phenomena, while Parkes has shown that in the mouse, normal cyclic œstrus may continue after the complete destruction of the follicular system by x-rays.

3. The third series of cyclic changes is the growth and retrogression of the corpus luteum. The corpus luteum elaborates a hormone or a series of hormones which have been supposed to be responsible for certain of the changes characteristic of pregnancy. Thus it has been supposed to control the growth of the mammary gland, although this fact has not been demonstrated clearly by experiment and recent work suggests that other factors are involved. The sensitization of the uterus for the reception of the fertilized ovum is probably due to the corpus luteum, since the typical pregnancy changes in the uterus can be produced in the ovariectomized animal by means of the injection of corpus luteum extracts, although even here other factors may be involved.

Numerous experiments clearly showed that the periodicity of these three cyclic changes in the ovary must be controlled not by the ovary itself but by some somatic tissue. If, for instance, we graft an ovary from an immature animal into an ovariectomized animal of the same species the grafted ovary will develop and will attain a state of maturity long before it could have done so in its original environment. Conversely, an adult ovary grafted into an immature ovariectomized animal does not exhibit the three series of cyclic changes. A suspicion that the somatic organ controlling the periodicity of the ovary might be the anterior pituitary arose from the frequency with which aberrations of sexual functions in women were observed to be associated with pituitary tumours. Clear proof that the anterior pituitary was this controlling organ was obtained from the work of H. M. Evans, Smith and Engle, and Ascheim and Zondek. It was found that if small pieces of anterior lobe tissue were mashed up and injected into an immature animal there resulted precocious œstrus, the maturation and ovulation

of a large number of follicles, and the growth of true corpora lutea. That is to say, the anterior pituitary had initiated precociously the three series of cyclic ovarian phenomena. When, on the other hand, large amounts of extract of anterior pituitary were injected, no œstrus and ovulation occurred, but only the formation of an immense number of corpora lutea atretica.

The opinion was widely held at one time that the luteinizing effect of the anterior pituitary was due to a different hormone from that causing œstrus and follicular maturation. The evidence for this is still not conclusive, and many workers on the subject are inclined to believe that only one anterior pituitary factor is involved.

Zondek and Ascheim showed that there was in the urine of pregnant women not only œstrin but also a substance having an action on the ovary similar to that of the anterior pituitary. This latter principle is usually termed *prolan*. The well known Ascheim-Zondek pregnancy test depends upon the presence of prolan in the urine. A similar substance also occurs in the placenta. The general effects of prolan and true anterior pituitary hormone on the ovary are similar, and the chemical properties are similar, but certain slight differences in physiological effect make it appear probable that the two principles are not identical. One view is that prolan is anterior pituitary hormone that has undergone some slight chemical change in the placenta. Further work is necessary before a decision can be reached.

Chemical work on these hormones has made disappointing progress. Something is known of their general properties; they are water-soluble; they are destroyed by heat, particularly when in solution; and they are probably of a protein-like nature. Marshall has carried out ultrafiltration experiments on prolan, and has suggested that it is a polypeptide of a molecular weight of about 800. Highly concentrated prolan preparations have been made by many workers, but so far no one has succeeded in isolating a chemically pure substance possessing the characteristic physiological activity.

The anterior lobe of the pituitary contains in addition to the ovary-stimulating hormone or hormones several other active principles. Recent work indicates that there is a hormone which directly stimulates mammary growth, even in the absence of the ovary, another which stimulates the thyroid gland, a third which stimulates the adrenal cortex, and a fourth which seems to play some rôle in carbohydrate metabolism. The latter appears to have an action antagonistic to that of insulin.

Special Articles

THE QUALITY OF THE HUMAN STOCK*

BY R. C. WALLACE,

President of the University of Alberta,

Edmonton

I would crave your indulgence this evening in dealing with a subject which a layman should hesitate to discuss before an audience representative of the medical skill of Canada. My justification is the importance of the subject, and my only valid qualification is that I am interested and concerned in all matters which have to do with the educability of men and women. I wish to discuss with you the quality of the human stock from the point of view of one who feels that there is no more urgent task that lies to hand than that of raising the quality of the human race. I wish to discuss it with you because you are all engaged in that very task from your own avenue of approach, and because you are by no means happy in the situation as it now exists. It may justify my appearing before you, in response to an invitation the cordiality of which I wish to acknowledge, if together this evening we may look at this problem from some of the points of view apart from those to which in your professional capacity you are restricted in your everyday duties.

It is almost a commonplace of modern thinking that there is an unjustifiable lack of uniformity between the progress which man has made in controlling the physical world and that which he has made in guiding human conduct. There is no excuse for the situation: but there are many reasons. Science has until very recently confined its attention almost exclusively to physical and biological phenomena, and has trod much less surely in the realm of the mind and the emotions. In this scientific age an exaggerated value has been placed on the material, in contradistinction to the spiritual. The results of scientific progress have been profound and revolutionary in the outward expression of living, in the trappings of modern civilization: that fact has distorted our perspective as to values. Science set its stage on the experimental mode: and to this a certain definiteness and concreteness, such as is found in chemical and physical processes and to a lesser extent in the simple biological processes, was necessary. Only today, and almost too late, do we realize that the same methods must be applied to the infinitely more difficult and elusive problems of human conduct

and human government as have been applied with such success to the non-personal world, if we are to go forward. It must be admitted that it has been our habit of mind as scientifically-minded people to look askance at the business of government and at those who practise it, without giving much thought to the contribution that the scientific approach and scientific training can make in this field. Our contribution has been almost negligible.

These considerations serve to explain, though they do not condone, our very halting progress in the realm of human affairs. But they are not all-sufficient reasons. Behind it all lies something more fundamental, to which I wish to address myself this evening. We are being satisfied with a mediocrity of quality, both physically and mentally, and this reflects itself in our imperfect ideals and limited progress. Science has done very much to raise the quality of the stock in the domesticated animals which man has reared for his service; it has done virtually nothing to raise the quality of the human stock. I do not wish to be misunderstood. I shall deal with what the field of medicine has accomplished. But in the matter of the quality of the stock, it is not an unfair statement that science has not yet made a contribution comparable at all in degree to what has been done elsewhere. It is a question of importance whether science is, or can be in the future, in a position to make such a contribution.

In order to place this problem in its correct setting, let me hasten to summarize what medical science has accomplished. There is a profoundly significant set of graphs in one of the studies which Mr. Hoover instituted through a research committee when President of the United States—that on Vitality in Recent Social Trends. The studies refer to the United States as a whole, or to limited parts of the United States, but in general terms they represent vitality conditions with which you are familiar as more or less universal in civilized communities which have had a century or more of scientific medical care. In the State of Massachusetts in 1800 the expectation of life at birth was slightly over thirty-five years for females, and slightly under thirty-five years for males. In 1929 it was 61 years for females and 58 years for males. That is the most profound fact which has faced the human race in a century of progress, and it is due to medical science. The situation is graphically analyzed in a series of illuminating studies. While the expectation of life has been increased twenty-five years in a century and a quarter, when such expectation is reckoned at birth, it is evident from the graphs that the life expecta-

* An address delivered to the Canadian Medical Association, at the Annual Banquet, Calgary, June 20, 1934.

tions of a man of 40 today is no greater than it was sixty years ago and at any higher age decidedly less. In other words, what has happened during the century of medical progress has been that children's diseases and epidemic invasions, such as typhoid fever, diphtheria, scarlet fever and pulmonary tuberculosis, have lost much of their terror, and our young people are being saved, but they are being saved at the cost of greater dangers after middle age than has hitherto been the lot of man. One of the most significant facts in the whole statistical study to which I refer is the increase in mortality during the period 1900-1929, both in males and females over the age of forty, from cancer, diabetes, cerebral hæmorrhage, heart disease, nephritis, and accidents. To the profession there is nothing new in what this study has brought out with startling clearness. The increased mortality rate above forty is due to several causes which cannot be easily disentangled. Nature's weeding-out process has not been permitted to proceed in the earlier years, and the types that survive until forty are not all hardy. The increased stress of life, particularly in the last thirty years, begins to tell more and more heavily after middle age in our present civilization. And the diseases which flesh falls heir to at that stage in life are, with the possible exception of cancer, not so amenable to medical science as are those which have been removed from the danger zone in the last century. They are diseases of degeneration, and it may be that medical skill will be able to do no more than postpone the evil day. There will be no possibility of doing what has been done for typhus or for diphtheria. What we have arrived at then, is a much greater chance of life for those who are born, but a lesser chance of old age for those who reach middle age. More youthful enthusiasm; less maturity of judgment ripened by experience. It is not necessarily a step in progress, measured by ultimate values, except in this very important matter, that disease in its most loathsome form has been practically banished. Much is still within practical reach, and will be achieved. The preventive field, so long the Cinderella in medicine, will tomorrow become the dominant idea in thinking and in practice: and measures of state or private health insurance will give powerful impetus to preventive work. The result will be still further to increase the average life expectation at time of birth, and there may even be considerable lessening of incidence of the degenerative diseases, if by periodic examination their early symptoms are detected in time for remedial action.

The moral foundation to the science the progress of which we have been reviewing is that life must be protected and saved, no matter how inferior in physical or mental quality that

life may be. It is obvious that on this basis nature's ruthless method of cleansing and purifying is interfered with; in the process of the prolongation of life, the life stream may become, not purer, but more muddled. The work of the medical man as such is therefore only a part of the larger public responsibility. If life is sacred, it is all the more important that life from the first be of high quality. To be well-born is our first duty; to remain well is our second. If we have the misfortune not to be well born, we will be nevertheless enticed into maturer life by medical aid, no matter how ill-fitted we may be to face it. It is this fact which makes of superlative significance the study of the practical and feasible steps which may be taken in the direction of higher quality in human stock—steps which it is not the primary responsibility of medical men to take, but where at least they can assist public opinion in making the choice. Let us first of all survey the difficulties in the way.

It has been relatively easy to apply what knowledge of genetics we now possess to the breeding of cattle, horses, and pigs. Man applies scientific principles most satisfactorily in an objective manner. When man himself is the subject of scientific application emotions colour the procedure, and scientific objectivity flies out through the window. Particularly is this so when religious scruples form part of the emotional complex. We may not expect that human breeding will be dealt with with scientific objectivity in the near future, if ever. It has been a step forward even to be able to discuss the matter; but in this realm, as in so many others, prejudice and emotion will make clear thinking difficult, and the interests of the human race will count for less than emotional or religious tenets. There is a further difficulty, and this within the scientific domain. In animal breeding our aim is to develop certain definite physical qualities, single qualities to which the established laws of heredity already give competent guidance to procedure. In the human race the concern is not only with physical qualities, but with mental qualities as well, where as a rule many factors are involved, and the inheritance conditions are less clearly established. While the hereditary character of intellectual qualities has been clearly established, the separate identity of the various qualities has not been established and traced through successive issue, as have, for instance, the colour of hair or the comparative length of limb in domestic animals.

Let us grant the difficulties both in the emotional and the scientific realm. Time is then needed in both departments, in the one case to spread the scientific viewpoint, to make eugenics not only a scientific philosophy but in very truth a religion, and in the other case to make possible the wider accumulation of data from the laboratory of the cytologist, the geneticist, the psycho-

logist and the psychiatrist. But that is not to say that there are not immediate problems. I propose to deal with some of them in the time that remains.

It is a characteristic feature of modern civilization that restriction in the size of the family has been most marked in the professional and intellectually most competent classes, and least pronounced in the unskilled classes and among people of foreign birth. There is general agreement that one of the important factors in this connection has been the relatively more widespread knowledge of methods of birth control among the professional classes than among the rural and foreign born classes. When all due allowance has been made for as yet unknown factors in inheritance, and while some weight must be attached to environment or nurture, the fact remains that children of the professional classes make a higher contribution through intellectual ability than those of the classes inferior in intellectual training. Terman, who has had a very wide experience in intelligence testing, tells us that superior intelligence is "approximately five times as common among children of superior social status as among children of inferior social status, the proportion among the former being about 24 per cent of all, and among the latter only 5 per cent of all". Moreover, the group of exceptionally intelligent children is made up almost entirely of children whose parents belong to the professional or very successful business class. An analysis of the women graduates of American eastern colleges has shown that the average number of children per married graduate is 1.4, and for all graduates 0.7, while the average number of children per woman of foreign parentage is 4.4. The statistics would point to the serious condition that, from the standpoint of intellectual quality, we are rapidly breeding out quality under present conditions. It is obvious that birth-control clinics should be equally available to all married people, irrespective of status, and that there should be no legal impediments, save only that the advice of a qualified physician should be necessary; otherwise, this disproportion in size of family is likely to continue, to the serious impairment of the quality of the human race. It is equally important that where the number of children in a professional class family is restricted for selfish reasons, an increasing eugenic race consciousness should be inculcated, in order that the wider social responsibilities should be more fully appreciated. Where economic factors are important in all probability greater allowance will have to be made for children than at present is provided for in salary or in taxation.

Over twelve years ago, Dr. Adami, a distinguished member of the McGill medical staff and later Vice-Chancellor of Liverpool University, made a proposal which in the intervening years has not had the attention which it de-

serves. He based his proposal on two well established facts; first, that intellectually and physically superior parents have children who are intellectually and physically above the mean; and secondly, that it was fully demonstrated in the raising of the United States army during the war that simple and effective machinery exists for intellectual and physical grading of large masses of the population. His proposal was that opportunity should be provided for intellectual and physical grading on a purely voluntary basis. It would come about naturally that the intellectually or physically superior would seek those of similar quality in marriage, and the highest level would thereby be maintained by natural selection. The proposal has much to recommend it, and may yet find favour when the importance of quality is more fully appreciated than is the case at the present time. That appreciation may come from a rational scientific outlook on the possibilities of human achievement in the hands of a sound and capable human stock. It will more probably be forced on us through economic necessity, which has been a salutary moulder of opinion in recent years. In a public address delivered by a prominent American medical authority last March, the following statement was made: "More than half of the institutional beds in the United States are now permanently occupied by individuals who are gross biological deficits, as far as society is concerned". The economic load on society which this involves will cripple, and may very soon stop, all progress; it may even submerge civilization. Through economic necessity we may become rational in our outlook. Even now, the mentally incapable and the habitual criminal are in some centres emasculated, and it is not without some measure of propriety that I deal with race quality at a medical convention in Alberta, for the province has been in the van in these measures in Canada. Here too the certification of fitness before marriage has been dealt with by the legislature. These are steps to a still far distant goal—that of a fitter, healthier, intellectually more capable people to do the world's work, which through its increasing difficulty calls for better quality of brain and brawn than has yet been given to the task. So may

"Man and his littleness perish, erased like an error
and cancelled
Man and his greatness survive, lost in the greatness
of God."

A final word of explanation must be said. It may appear worthy of comment that one who is in the field of education should lay such stress on the qualities which come through inheritance. Is it not the case that the very philosophy of education rests on the foundation of the moulding of man in intellectual and moral quality through environment and through

training? Can it be that we are losing hope in our work, and are turning with a despairing gesture to something that is so very far off that it runs the risk of being called visionary. Not so. It is only that the task is otherwise that of Sisyphus. The stone rolls back with each new generation's birth, and must be pushed anew up the hill. Nurture can do much for the individual; otherwise, educationists would seek other vocations. But they are not convinced that the individual can transmit any quality which he has acquired to his progeny by inheritance. It is a higher datum plane from which to measure that they seek. That can come only from a higher quality of stock. Then can nature and nurture go together to higher achievement. The eugenist, the medical man, whether preventive or remedial, and the educationist can thus together build for better things. As Horace has it

"The brave are born from the brave and good. In steers and horses is to be found the excellence of their sires; nor do savage eagles produce a peaceful dove."

That emphasis on inheritance has not been modified by the results of scientific investigation since the time of Horace. It is still the profoundly significant fact. When we are fully seized of the consequences, the difficulties now in the way to better breeding will disappear; for truth is mighty and will prevail.

THE HOT SPRINGS AT BANFF, ALBERTA

By J. D. ROBINSON,

Banff

Medical men attending the Canadian Medical Convention at Calgary this year had a wonderful opportunity to visit Banff, which is known the world over as a summer resort of the highest class. But Banff is also a health resort, because of its clear brisk air and the hot mineral springs which issue from Sulphur Mountain. These waters contain many salts and minerals which are beneficial in health and disease. The waters also have radium emanation. Spas in Europe having radium emanation are those specifically used in the treatment of arthritis, and hot mineral springs have a reputation known and accepted everywhere for their efficacy in the treatment of arthritis and rheumatism.

Banff Hot Springs have been developed more for treatment purposes, probably, than any other thermal springs in Canada. Years ago at the Upper Hot Springs many hundreds of crutches were collected as evidence that many people who had come to the baths as cripples were able after treatment to go away without extraneous aid. All sorts of cases are treated at the Banff Mineral Springs Hospital, but those which

receive special benefit from the waters are chronic arthritis, articular rheumatism, spinal arthritis, chronic nephritis, anæmia, and neurasthenia.

The action of the warm baths in arthritis is that the circulation around the joints is improved and exudates are softened and absorbed. Warm baths of 101° F. and over are used. Depending on the patient's physical condition, a routine such as the following is typical—a warm bath for fifteen minutes or more; the hot steam room, where vapour is inhaled and toxins exhaled for ten minutes; the hot dry room for ten or fifteen minutes; then the patient is taken to the cooling room where he is blanketed and rests until he is ready for massage and manipulation; following this, rest in bed for an hour or more. Manipulation and friction are sometimes carried on while the patient is in the water bath, as at this time the joints are less painful and movements can be carried on more effectively.

As warm or hot baths of even a mild type may cause an increase in pain primarily in gouty and arthritic joints, patients must be forewarned of this when commencing treatment; otherwise they may become discouraged, believing that they are becoming worse. This reaction is in reality of good omen, and usually indicates that exudates will be removed and improvement may eventually be expected. The mental attitude of the patient has a great deal to do with his improvement and treatment. It is necessary for the physician to have his whole-hearted cooperation in order to get the best results.

In Canada, where hydrotherapy has not been studied and developed so strongly as in the older countries we find a great many patients coming to the baths after they have tried everything else. This does not give hydrotherapy or the medical attendants a fair chance to show what can be done. If physicians who have cases of the kind mentioned would refer them early after diagnosis it would be possible to lessen greatly the numbers of cases which go on to invalidism. Hydrotherapy is the rational basic treatment for arthritis. It seems that no other treatment does, or has done, so much for these sufferers. The advantages of treatment in an institution such as the Banff Mineral Springs Hospital are as follows. Patients are removed from their ordinary environment. They leave behind them their business worries and mental loads, and have come prepared to give their undivided attention to the process of getting well. Hydrotherapy institutions are prepared to look after cases of the kind mentioned and have the equipment along with the trained attendants necessary, to see that treatments are carried out as prescribed. This cannot be done in the home. At Banff, with the wonderful mountain air, the scenery, the hot mineral baths, and the restfulness, there is a great impetus to get well.

The treatment is under medical supervision. It is a mistake to think that one can get benefit from a short course of baths. Hydrotherapy is a most efficient treatment but it is slow. It must be persisted in, and the medical man who recommends spa treatment should make this clear to the patient. The general examination, including examination of the heart and the estimation of blood pressure, is important and should not be neglected on the arrival of each patient, to determine the type and severity of the treatment which is most suitable. It is common knowledge that a body placed in a prolonged hot water bath will have a sharp rise in temperature, taking up heat from the water until equal with it. This is because the body is prevented from controlling its temperature by the usual method of evaporation. Red blood cells are increased on going to a higher altitude, and are also increased with a stimulation of the vasomotor system. Stimulation of the vasomotor system is brought about by the use of hot and cold water baths, used alternately, and should always be under the direct supervision of a medical man. Toxins are eliminated through the lungs, skin, bowels and kidneys after hot water baths, but the greatest discharge is through the skin and lungs. Exudates are softened and absorbed through improved circulation; joints are less painful and much more mobile during the bath. Massage should be used regularly in chronic arthritis, to prevent atrophy of the muscles due to decreased use of the joint. Passive movement and massage may be used while the patient is in the bath, and, later, active movements may be instituted.

Summing up. While a great deal has been done, and many hundreds of people who have been afflicted with types of rheumatism and

arthritis have received benefit and relief from their painful conditions at hydropathic institutions, one feels that a great deal more will be accomplished when medical men realize more fully that most of their arthritics of all kinds will improve more completely under hydrotherapeutic measures than under any other, and many of them will get quite well. Also, that spa treatment is more satisfactory than home treatment, because of the change of environment, special equipment, trained attendants, routine, restfulness, and last, but not least, the beneficial effect of the hot mineral springs water.

It will be noticed that only hydrotherapy has been mentioned. We know that many cases of arthritis have as their origin, infective foci in teeth, tonsils, sinuses and intestinal tract. These foci must, of course, be attended to before one can expect improvement. Also electrotherapy and many drugs and preparations are being used to help effect a cure or improvement. Those which have been found useful have their place in the therapy instituted at health resorts, though the basic treatment is hydrotherapy.

One hopes that in a very short time an association may be formed in Canada, having as its basis of membership medical men who are connected with hydrotherapy establishments in the Dominion. Through this association the many advantages of spa treatment may be brought to the notice of Canadian medical practitioners. Canadian springs compare favourably with European watering places and health resorts. So far, their value has not been sufficiently recognized. Organization, education and development will raise them to their proper place.

Men and Books

THE KNIGHTS OF THE ORDER OF ST. JOHN OF JERUSALEM IN CANADA UNDER THE FRENCH REGIME

BY MAJOR-GENERAL G. CARLTON JONES,
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Branch of the Association*

When the question of preparing a paper on the part the Knights of St. John played in the founding and early history of Canada suggested itself to me, I did not realize that I would be only re-opening an old discussion which had taken place about thirty years ago in the press of Quebec. I think, however, it is well that this matter should be recorded as part of the

present development of the English order in Canada.

We find in the early history of New France strong evidence of the political machine work of the Knights of Malta. So strong is the evidence that one authority believes that it was intended to establish the order in Canada as the controlling interest in the Colony, if not its actual proprietor. De Montmagny, Champlain's successor, was to be the instrument. It is thus possible to explain Montmagny's peculiar actions by supposing that he was working in the interest of the Order rather than of the King of France. He may have been working in conjunction, under orders from the Grand Master, with de Poincy, the Governor-General of the French West Indies and De Razilly, the Governor of Acadia, all being Knights of St. John.

De Poincy, when recalled by the King of

France, refused to budge. He had fortified the Island of St. Kitts and had built several war ships. He was supported by the Grand Master, and as a result of negotiations with the French King, the Islands of St. Kitts, St. Croix, and others were purchased by the Order for £5,000. De Poincy, a Grand Cross of St. John, was a very old man and died soon after, and the islands were sold to a company of merchants in 1665. This seems to be the only time that the Sovereign Order of Malta actually established itself in the new world by the possession of territory.

An effort was made, however, by De Razilly to found a priory of the Order in Acadia, for on the 8th of September, 1635, he wrote to the Grand Master asking authority to establish a priory in Acadia, probably at the site where Halifax now is, as it was to form a Naval Station for the Order, for the building of ships and for the general operation of the maritime affairs of the Knights. The Grand Master, while commending his zeal, replied that there were no funds available owing to the huge expenditure placed at that moment on the Order by its ceaseless combat with the Ottoman Empire. De Razilly died two years afterward. Soon after the despatch of this letter from Malta, Montmagny was sent to Quebec as Governor to relieve Champlain, who had, however, died on the Christmas Day previous. Champlain was not a Knight of Malta, though he had been selected for the work in Canada by one high in the Order and a proprietor of the Colony, the Commander de Chaste, Governor of Dieppe; Brasdefer de Chasteaufort, who was interim Governor after the death of Champlain, and before the arrival of Montmagny, was of the Order. With Montmagny came his Lieutenant, De Lisle, also a Knight. Soon after there became interested in Canada one of the most notable Knights of the Order, Brulart de Sillery, who founded near Quebec, in 1637, a chapel, a convent, a hospital, and dwellings for converted Indians. The money came from his commandery at Troyes.

Quebec under the rule of Montmagny and his associates was practically a religious community. The influence of the Order of Malta was felt everywhere, and it is stated by several historical authorities that the reason of the sudden recall of Montmagny was that the French King became suspicious of his obvious work in the interest of the order to which he belonged.

Did Montmagny establish a priory or commandery at Quebec? You have no doubt noticed a stone set in the archway of the Chateau Frontenac, bearing the cross of St. John and the date 1647. Around this stone has been woven the romance of the establishment of a priory of Knights at Quebec, which has been strengthened by two separate references by contemporary writers to a house of the Knights-

Hospitallers in that town. Knox, in his wonderful journal of the wars in Canada of 1759-60, in an entry made after the taking of Quebec, mentions an imposing house not yet finished for the Knights Hospitallers. The second reference is in the *American Gazetteer* of 1763, which mentions the priory of the Knights of Jerusalem, a superb building in stone, which had cost, it is said, 40,000 pounds sterling. Perhaps this last reference is to the Hotel Dieu, the nuns being called Hospitalières. That may be so. But how explain Knox? He refers in this same sentence to the Hôtel-Dieu, and is absolutely correct as to all other buildings. He spent eight months in Quebec, and was a keen observer. We take his evidence on all other matters connected with the stirring events of this winter, why should we not do so in this? There is, however, a weak point, for in a subsequent entry about Montreal, he refers to a similar house at that place, evidently mistaking the convent there. But he was only a few days in Montreal, and did not know the place as he knew Quebec. The stone I have referred to was found in 1784, when workmen were building the courtyard of the old Chateau St. Louis. The Abbé Bois states that "the Knights of St. John of Jerusalem, Montmagny, Brasdefer, Sillery, and others in Quebec, had erected a Bureau in the courtyard of the Chateau St. Louis; it had cost 40,000 livres—French, not pounds. The gable contained a large stone, set in the wall, on which were engraved the arms of the order, this stone having dropped to the ground when the house was destroyed by fire in 1759, during the siege, where it remained until 1784." It is interesting to note that a hill behind the present Military Hospital was called Mont Carmel, a name closely associated with the Order.

There is no evidence amongst the Archives of the Order to show that either a priory or commandery was officially established in Quebec. But I think that we can reasonably conclude that a house or bureau for those knights who were at the head of affairs in the Colony, under the rule of Montmagny, was constructed. It is not likely that such ardent and pious members of the Order as the Governor and De Sillery would spend those long years in Quebec without having some place dedicated to the fraternity which they loved and served.—Reprinted from *Canadian First Aid*, Nov., 1933, p. 11.

FRANKLIN'S INSCRIPTION FOR THE PENNSYLVANIA HOSPITAL

The *New York Times* of February 28, 1933, has the following comment on Franklin's inscription for the corner-stone of the Pennsylvania Hospital, Philadelphia.

"Benjamin Franklin is so much the sage and statesman that people are apt to forget what a first-rate literary draftsman he was. No man,

said Doctor Johnson, is on his oath in a lapidary inscription, and certainly few men are at their ease in composing any kind of inscription. But the legend which Franklin composed for the corner-stone of the Pennsylvania Hospital—the original manuscript turned up recently in Germany — shows how feeling, grace, and decorum may dwell together in one who is a master of style.

"It is as follows:

In the Year of Christ
1755

George the Second happily reigning
(For he sought the Happiness of his People)
Philadelphia flourishing
(For its Inhabitants were publick-spirited)
This Building,
By the Bounty of the Government
And of many private Persons,
Was piously founded,
For the Relief of the Sick and Miserable.
May the God of Mercies
Bless the Undertaking!"

—*The Diplomat*, 1934, 6: 85.

Association Notes

The Sixty-fifth Annual Meeting of the Canadian Medical Association

The Section of the History of Medicine met on the morning of Thursday, June 21st, with Dr. H. C. Jamieson, of Edmonton, in the Chair. Dr. W. W. Francis, of Montreal, was elected President of the Section for 1935 and Dr. H. E. MacDermot, Secretary.

Dr. Jamieson had prepared a paper on "The pioneer doctor of Alberta", but, with much self-abnegation, in view of the lengthy program, he refrained from reading it. However, a short abstract is now given.

The first medical practitioner in Alberta was Dr. W. M. Mackay, who arrived at York Factory by boat in 1864 as surgeon for the Hudson's Bay Company. Three years after his arrival, he moved to Fort Chipewyan, and later to Dunvegan in the Peace River district. He was made chief trader in 1879 and retired to Edmonton in 1898, where he died in 1915. Dr. Mackay received his tuition from a number of the foremost medical men of the day, including Sir James Y. Simpson, Professor John Goodsir, a cousin of the late Dr. H. Goodsir Mackid, of Calgary, and Professor Syme.

The first hospital in Alberta was opened at Fort Macleod by the North West Mounted Police, and Dr. E. A. Braithwaite, now chief coroner for the province and the oldest active practitioner in the province, was the first patient.

The first reference to Calgary hospitals was in the diary of Assistant Surgeon Nevitt, attached to the North West Mounted Police, as of March 18, 1877. Dr. Nevitt said: "The kits, arms, stores and everything inspected. The hospital looks well. Lauder seems to have pretty nearly all he requires. He handed me a list of things absolutely required." The hospital was opened shortly afterward in a frame house. The first general hospital was opened in 1894 and the Grey Nuns opened the Holy Cross Hospital, also in a frame house, in 1891. The first graduate nurse of the Calgary General Hospital was Marion Moodie, in 1898.

Dr. T. A. Patrick, of Yorkton, Sask., presented some "Reminiscences of a pioneer Saskatchewan doctor, 1889-1919". He gave a full and graphic account of medical practice in his province in the early days, culling largely from his own experience. His difficulties were great, and he seems to have become a specialist on hernia!

Dr. E. P. Scarlett, of Calgary, read a most interesting paper, of a literary flavour, on "Satire in medicine". This title might have been turned about, "Medicine in satire". The paper evinced a wealth of reading and an enviable acquaintance with the doctor and medical practice as they appear to the layman. This paper will appear shortly in the *Journal*.

Dr. A. G. Nicholls, the Editor of the *Canadian Medical Association Journal*, read a paper entitled "De Blegny and the first medical periodical". This can be found in the *Journal* for August, page 198.

The Section of Military Medicine met informally at a luncheon given at the Palliser Hotel by Dr. J. N. Gunn, D.S.O. The luncheon was attended by overseas officers and officers of the non-permanent medical service and the chief topic for consideration was the problem that would confront Canadian doctors in the event of another war—the care of the wounded, the counteracting of medical weapons of offense in the hands of the enemy, and the mobilization of a Medical Army Corps.

Unanimous endorsement of a resolution providing for the recruiting of medical men in the event of war featured the luncheon-meeting. It will go to Council for consideration from this Section. In view of the mobilization in 1914, which recruited medical men in the order in which they applied, thereby taking most of the specialists from hospitals, offering serious impairment to medical college staffs, and abolishing health services in many districts, the resolution suggested that the Canadian Defense Council devise some plan to function immediately on mobilization. It would provide that recruiting be governed by a committee of three in each

district, comprising the medical health officer and two medical men of high repute, the latter to be named annually by the Canadian Medical Association. This committee would be held responsible for the selection of suitable medical men for the army's requirements, leaving enough to carry on hospital, college, and civic medical work in each district. Col. J. T. Clarke, of Ottawa, moved the adoption of this resolution, which had Lt.-Col. A. R. Haggerman as its seconder. Dr. F. A. C. Scrimger, V.C., of Montreal, spoke to the motion.

"One of the best means of keeping up an army's morale lies in its reassurance that there are the means and the will to move wounded soldiers out of the zone of great danger into one of comparative safety, and that, once there, they may be made fit as soon as possible," said Major T. C. Clarke, M.C., M.D., C.M., whose address on "A glimpse of the past: what of the future?" featured the luncheon hour. Necessity for mobility and surprise as factors in the campaign were emphasized by the speaker, who told of the secrecy and rapidity of movements in one World War engagement. Defects in transportation and heavy shelling by the enemy had been hindrances to clearing the wounded. What of the future, then? he asked.

"The principles of evacuation of the wounded remain the same. A highly mechanized mobile force is essential. The forward units of the medical service must then be prepared to advance as rapidly as the men for whom the service will care, and evacuate as quickly." All field ambulances should be as carefully mechanized and be conveyed by vehicles capable of moving rapidly over all sorts of roads, and crossing everything but a deep river.

Transportation of the wounded by air had received serious consideration since 1918. No type of plane, reasonably crash-proof and capable of carrying a reasonable load had been evolved, however; added to which were the improbabilities of finding proper landing and loading fields and the undependability of weather. The motor cycle remained a possibility in the clearing work.

Col. A. E. Snell, D.M.S., Ottawa, in the discussion which followed Major Clarke's paper commented upon the need for entirely armoured or tank brigades and the possibilities of air ambulance service, which he declared deserved much consideration on the part of the medical people. The unlikelihood of finding a field sufficiently smooth to land upon, coupled with the psychological and physiological problems of airplane transport for the wounded, made these problems difficult of solution.

Sir Frederick Banting hoped the Canadian Medical Association would establish a department of military warfare, in continuing the discussion. Quoting a personal friend of

Chancellor Hitler, Sir Frederick declared that no war could occur in Europe within five years, since till then Germany would be unprepared. Radio-control of planes for bombing in another war would make the real decision of the campaign 15,000 feet above the earth, he believed. The use of communicable diseases as a means of warfare, such as had been attempted at the close of the last war, promised to make a future conflict one of annihilation. "I should hate to see such methods introduced, but, if they are, we must be in a position to combat them", he continued. Malaria, yellow-fever, cholera and nerve disorders in the hands of the enemy would spell disaster for an army and civilian population alike.

Dr. Gunn, who introduced the speakers on this occasion, paid tribute to the disinfection work of Dr. Harold Orr, of Edmonton, which, in his opinion had done more for the comfort of the soldiers than any other one man's contribution during the World War.

The chief interest on Thursday afternoon centred about the subject of cancer, which was dealt with extensively by Drs. A. Primrose, Toronto, W. J. Deadman, Hamilton, D. C. Balfour, Rochester, Minn. and E. E. Shepley, Saskatoon. In view of the importance of the subject and in order to aid in the proposed establishment of a "Cancer Campaign" for Canada these papers will be published together and in full in the *Journal*.

On Friday morning papers were read by Dr. Wm. Webster, of Winnipeg, on "The relative merit of nitrous oxide and ethylene"; Dr. Geo. S. Young, Toronto, on "The differential diagnosis of coma"; and Urban J. Gareau, Regina, on "Twenty-three cases of acrodynia".

Dr. Webster gave a short critical comparison of the virtues and vices of the two gases, and a more lengthy consideration of the subject of inflammability of anæsthetic gases, and detailed thoroughly the appropriate measures to be adopted for combating it. Dr. Young's paper appears in this issue of the *Journal* (see page 381).

Dr. Gareau's paper was of special importance, as he has been able to study a larger number of cases of acrodynia than have others in Canada, apparently. His paper will be published in full, later. Important features of this Session were a symposium on "Sexual sterilization: four years' experience under the Act of Alberta". Dr. C. A. Barrager, of Edmonton, dealt with the subject for himself and his colleagues, Drs. G. A. Davidson, Ponoka, W. J. McAllister, Oliver, and D. L. McCullough, Red Deer; also, a clear and explicit presentation of "Recent advances in the physiology of the pituitary gland", by Prof. J. B. Collip, of Montreal. This session was apparently very popular as the room was crowded.

Dr. Barrager presented his subject in a most complete and scientific way, illustrating his statements by a wealth of tables and statistics. He reminded his hearers that many operations, made necessary in the interests of patients' bodily health, incidentally resulted in sexual sterility, and yet these were being frequently performed by surgeons throughout Canada and elsewhere, and had been so performed for many years. They were and had always been accepted as a matter of course by both surgeons and patients. The operations for sterilization under the Act were exactly the same as some of these, except that sterilization was the main purpose of the operation, in as much as sterilization was necessary in the interest of the health and welfare of the race, which was surely as important as the health and welfare of the individual. In many cases, of course, both the welfare of the individual and of the race were at stake, only the welfare of the race was the chief end.

Though some thirty states in the American Union had laws permitting sterilization, and though Switzerland had had sterilization laws for years, the Province of Alberta was the pioneer in the British Commonwealth of Nations to enact such a law, which was assented to in 1928. According to the speaker, up to the end of 1933, a total of 288 cases had been approved by the Eugenics Board, without whose authority no operation could be performed.

The Eugenics Board consists of four residents of Alberta, Dr. J. M. MacEachran, of the University of Alberta, chairman; Dr. E. L. Pope, professor of medicine in the University of Alberta; Dr. E. G. Mason, Calgary, and Mrs. Jean H. Field, of Spurfild.

The operations themselves had been uneventful and rarely followed by even minor complaints, and there had been no serious complaints. In the male, of course, the operation is a very slight one, and even in the female it is less serious than childbirth itself. No organs are removed, and there is no mutilation, and the patient suffers no change in either feelings or appearance; hence the operation is less serious for the patient than most of the operations that have to be performed for bodily disease.

Two great classes of patients have been so treated. The first of these, and the class to which the greatest number of patients belonged, were those of subnormal mental development, who by reason of that defect were unable to properly care for themselves in the social group, and certainly quite unfit to have the serious responsibility of bearing and rearing children. Though each of these cases was presented to the Board on its merits, the speaker showed that great social problems, particularly of immorality, illegitimacy and delinquency, were intimately linked up with the mental defect, and particularly so in the cases under discussion. Not only for the sake of the community at large was it most undesirable that such persons should bring

into the world children doubly handicapped both as to heredity and upbringing or home environment, but it was unfair to the patients themselves that they should be permitted to assume or have thrust upon them a responsibility they were wholly unfit to carry.

There was also the other class, those unfortunate men and women who had suffered serious mental breakdowns, and for whom no doctor would recommend parenthood, and would likely, in fact, forbid marriage if it meant parenthood—this partly because of the danger of the transmission of the tendency to mental disease or defect to the children, partly because of the risk in the case of a woman of further breakdowns, and, partly, the grave likelihood of any children born to the patient being deprived of full and normal parental care. If we permit patients to decide to have operations resulting in sterility because of bodily disease, surely we should permit them to have the same operation to avoid transmitting mental disease. That heredity in these two groups was a matter that had to be seriously reckoned with was shown by the fact that in over 60 per cent of cases passed by the Board there was evidence of serious mental or nervous disease in the family record.

The condition of most of the children already born to patients passed by the Board was unknown. But it was shown that, even if all these were, physically-speaking, normal, the proportion definitely showing mental defect or instability was unduly large, much larger than for the population in general. The outlook for these children, in general, was therefore not good.

It has been shown definitely in Alberta that the fear that sterilization would increase promiscuity or lower moral standards of the patients concerned was unfounded. In fact the reverse seemed to be true.

"The rights of the individual and the provisions of the law are being adequately safeguarded by the fact that all authority rests with a Board composed of persons of high repute, by the great care observed in the selection of cases by the medical officers of the department, and by the fact that consent is required." Consent, he stated, meant the consent of the patient, or, if incompetent to give consent, then that of the parent or guardian, or, if married, of the husband or wife, or if there were no parent, guardian, husband or wife resident in the province, the consent of the Minister of Health.

Evidence has shown overwhelmingly that sterilization is a sound, humane and effective procedure, and is one of the chief means of coping with the grave problem of the increasingly large number of mentally sick and mentally deficient persons that each province is being called upon to care for. The work carried on under the Act is proceeding smoothly and is in Alberta growing steadily in favour with those who have the public welfare at heart.

Dr. J. B. Collip, in his paper, noted that in many cases treated over a long period with some glandular extract a state may develop varying from a lessened to a complete lack of response. Likewise, some untreated cases do not respond to injections of a known potent glandular extract. During the past two years an extensive study had been made under his direction upon an extract of the anterior pituitary gland. It was clearly proved that animals treated for some weeks with this hormone extract became non-reactive to it. In addition, it was also found that if the blood serum of these non-reactive animals was injected into normal animals these latter animals became non-reactive. Further evidence has been obtained which would tend to show that inhibitory substances for various hormones may appear in the blood of animals treated with different hormone extracts.

"The production of a serum inhibitory to a specific hormone may be viewed in one of two ways. Either the administered hormone extract is acting as an antigen and the inhibitory substance which can be detected in the blood serum of the treated animal is an antibody, or else the inhibitory substance represents a normal constituent of the blood which under normal conditions is balanced, as it were, against the respective hormone in such a manner as to be masked itself. We prefer this latter view." This broad principle is particularly attractive, since it may be used to explain such things as the great difference in the responsiveness of different species to hormone as well as minor variations in responsiveness within a species.

In view of the fact that there are many examples of extreme variations in the response of an individual of one species to an administered hormone as compared to the response of an individual of another species similarly treated, he was led to postulate in his Welch lecture, a few weeks ago, the theory of inverse response. "The responsiveness of an individual to administered hormone varies inversely with the hormone content or production of the individual's own gland."

While the results of these recent investigations in the laboratory suggest that many dangers may attend the clinical use of glandular extracts, nevertheless they point the way to new applications. If the general principles established by the experimental work are applicable to the human subject then the possibility must be considered of producing inhibitory hormones in an active way in the system of the patient, or of raising the level of these in a passive way by the use of active extracts of inhibitory sera, the latter produced from horses injected over long periods with adequate amounts of the purified hormones.

On Friday afternoon a most instructive and well-planned symposium was held on "Cardio-vascular disease" in which Drs. Duncan Graham, Toronto, John Oille, Toronto, C. C. Birchard, Montreal, and John Hepburn, Toronto, took part. Their papers will be published, together, in the *Journal* shortly.

In the Section of the Eye, Ear, Nose and Throat, on Wednesday and Thursday, several valuable papers were presented, among them "The treatment of glaucoma", by Dr. S. R. Gifford, Chicago; "Contusions of the eyeball", by Dr. W. Harold Brown, Edmonton, and "Corneal infections", by Dr. Gifford. These papers will appear in the *Journal* in due course. On Wednesday afternoon a valuable symposium on "The relationship of the radiologist to some phases of medical practice", was conducted by Drs. B. J. Harrison, Vancouver, E. E. Shepley, Saskatoon, C. W. Prowd, Vancouver, and C. M. Henry, Regina.

In the Section of Urology excellent papers were presented by Drs. Emerson C. Smith, Edmonton, on "Arterio-venous aneurysm of the renal pedicle"; Frank S. Patch, Montreal, "Cystine nephrolithiasis"; H. D. Morse, Winnipeg, on "Transurethral prostatic resection", and A. B. Hawthorne, Montreal, on "Sarcoma of the prostate". Dr. Patch's article can be found in the September *Journal*, (see page 250).

Hospital Service Department Notes

The Ethics of Ectopic Operations

Those members of the medical profession who attend Roman Catholic patients or who are on the staff of Sisters' hospitals will be much interested in a recent pronouncement upon the ethics of ectopic operations, an interpretation which bears the imprimatur of His Eminence the Cardinal Archbishop of Chicago and of others.* This exposition may help to solve a very vexed question, particularly in those hospitals where the interpretation of the moral question at issue has been particularly rigid.

The author, Father Bouscaren, a Jesuit, and Professor of Canon Law in an Illinois seminary, reviews most exhaustively the principles involved and the arguments for and against the teaching of the Church. The Holy Office has decreed that any surgical operation which is a direct killing

* Ethics of Ectopic Operations. Rev. Timothy L. Bouscaren, S.J., Loyola University Press, Chicago.

All communications intended for the Department of Hospital Service of the Canadian Medical Association should be addressed to Dr. Harvey Agnew, 184 College Street, Toronto.

of the child, and this would include the direct removal of an immature fetus, whether uterine or ectopic, is wrong and never permissible. However, it is admitted that theologians are not agreed as to whether or not a pregnant tube may be removed to save the mother's life before it has actually ruptured. Lehmkuhl, Genicot and Vermeersch take the liberal view that it is the mother's diseased organ, not the fetus, which is being removed and, as the death of the fetus is only an indirect consequence, the excision of a tube containing a non-viable fetus may be allowed when the necessity for so doing is urgent. Antonelli, Noldin-Schmitt and Sabetti-Barrett cling to the more severe opinion, denying the licitness of the operation under any pressure of necessity. Others take the view that until the tube is actually ruptured the removal of the tube enclosing a living and non-viable fetus is always and necessarily illicit.

Father Bousearen argues that (1) when the pregnant tube is removed, the death of the fetus is produced only indirectly; (2) while originally the pregnancy was the cause of danger, the immediate danger is the presence of a disorganized tube; (3) this indirect removal is licit when there is a proportionately grave cause for the operation, and this grave cause may exist before as well as after actual rupture, as the likelihood of viability of the fetus with deferred operation is extremely meagre, the notably greater probability of saving the mother's life by tubal excision would be a proportionately grave reason for operating; (4) the gravity of the reasons for interfering would vary with (a) whether or not the mother can be kept under competent observation, (b) the condition present when the ectopic is discovered in the course of a laparotomy for another disease, and (c) when the pregnancy has continued for four or five months without tubal rupture or a secondary abdominal pregnancy has taken place. An additional argument advanced for certain cases is the increased opportunity which the operation may afford of conferring baptism on the child while still alive.

The author summarizes: "The removal of a pregnant Fallopian tube containing a non-viable living fetus, even before the external rupture of the tube, can be done in such a way that the consequent death of the fetus will be produced only indirectly. Such an operation may be licitly performed if all the circumstances are such that the necessity for the operation is, in moral estimation, proportionate to the evil effect permitted. But in all such operations, if the fetus be probably alive, care must be taken to baptize the fetus immediately, at least conditionally." Repeatedly in his conclusion he states "If a present operation offers a notably greater probability of saving the mother's life, the operation will be permissible." The study and its conclusions have been most favourably

commented upon in *Hospital Progress*, the official journal of the Catholic Hospital Association, by Rev. A. M. Schwitalla, the President of that body.

Discounts by Hospitals to Doctors, Nurses and the Clergy

The practice of giving discounts or other special consideration to doctors, nurses or the clergy is one concerning which hospital administrators have frequently written our Department of Hospital Service. Recently, to obtain a general picture of the prevailing practice, information was obtained from 20 representative public hospitals in Canada as to the arrangement in such institutions. A much abbreviated summary of the twenty replies is as follows.

For members of the medical staff.—Five made no charge; 5 gave a 50 per cent reduction; 4 made a 25 per cent reduction (three with no extras); 1 made a 20 per cent reduction; 2 charged room rate only without any extras. In nearly all cases, these reductions applied to the families also. Several reported considerable flexibility, depending upon the circumstances.

For non-staff doctors and families.—One hospital made no charge; 2 gave a 50 per cent reduction (one charging the family regular rates); 4 gave a 25 per cent reduction; 1 a 20 per cent reduction; 2 omitted extras.

For nurses on hospital staff.—Seventeen hospitals provided free hospitalization, and 3 gave a 50 per cent reduction. In quite a number of hospitals the graduates of that particular school have their hospitalization expenses cared for by the Alumnae through a special fund. In 1 hospital there is a 25 per cent reduction after one month's care.

For nurses not on Hospital Staff.—The arrangement varies according to whether or not the nurse is a graduate of that hospital and in practice. If a graduate, her expenses may be met by the sick benefit society. Apart from these arrangements, 12 give their alumnae 50 per cent reduction, of which number 5 give the same reduction to all outside nurses. Four give a 25 per cent reduction to non-staff nurses, 1 of which (included above) gives a 50 per cent reduction to its own graduates. One takes off extras and 1 always gives special consideration. Two charge all outside nurses regular rates and 4 charge non-graduates only regular rates.

For the sub-staff.—Considered broadly, 18 of the twenty hospitals give the sub-staff, clerks, orderlies, maids, etc., free hospitalization. Two hospitals charge regular rates, although one waives extras. To those living out, 1 charges regular rates and 1 charges clerks and stenographers half rates. Some have regulations grading the free hospitalization according to length of employment, etc. While most provide

public accommodation a few provide semi-private space.

For the clergy.—Thirteen hospitals give no special discount for the clergy; 5 do give a 25 per cent reduction (or a private room at semi-private rate) and 2 hospitals give special consideration when requested.

Medical Societies

The Meeting of the International Society for Geographic Pathology, held at Utrecht, Holland, July 25 to 28, 1934

This Society meets every three years, the present meeting being the second since its foundation. The entire meeting, extending over a period of three days, was occupied in a discussion of the problem of arteriosclerosis. There were 160 representatives present from all quarters of the globe, two being from Canada and seven from the United States. The program was of the nature of a symposium for which some of the leaders in the study of arteriosclerosis had been selected to present the various phases of the subject. Dr. Klotz, one of the representatives from Canada, was entrusted with presentation of the topic "Experimental arteriosclerosis and its significance in human arteriosclerosis". Anitschow, of Russia, dealt with "Histopathology and pathogenesis of human arteriosclerosis", while Staehelin, of Switzerland, presented the clinical aspects of the disease. Dr. Fox, of Philadelphia, gave his findings in respect to the occurrence of arteriosclerosis in wild animals living in captivity in zoological gardens. Dr. Diaz, of Spain, discussed the treatment and prophylaxis of arteriosclerosis, pointing out that as the condition arteriosclerosis itself did not give rise to clinical manifestations, the treatment was largely related to the organs and structures suffering the effects of an altered circulation brought about by the changes in the arteries.

A discussion of the papers was entered upon by Aschoff, Askanazy, Fahr, Leary (Boston), Roussy (Paris), de Josselin de Jong (Holland), Henschen (Sweden), and many others. The consensus was that the studies both in experimental and human pathology indicated that arteriosclerosis is a disease of a variety of types, involving the intima, the media; and at times the adventitia; that it does not always begin in the same way; and that there is a variety of factors which may bring about these several lesions.

The desire on the part of some schools of thought to limit the term arteriosclerosis to the type of lesion described by Marchand as arterio-

sclerosis was only supported by a few. It was felt that there was no justification in redefining the term arteriosclerosis to suit the interpretation of a few. Further, there is evidence that factors of intoxication, infection, fatigue and altered metabolism play important rôles in initiating and further developing lesions in arteries; and that the claim that arteriosclerosis is the outcome of dietary indiscretions or temporary metabolic disturbances in otherwise normal individuals, had insufficient proof. The interpretation of the animal experiments performed upon the rabbit (fed on fats and cholesterol), cannot be directly applied to man, and the lesions arising in the rabbit do not represent hyper-physiological events. The fat and cholesterol deposited in the so-called arteriosclerotic lesion of the rabbit aorta are not the cause of the arteriosclerotic process but rather an index of the antecedent degenerative process in the vessel wall.

The delegates and representatives attending the meetings were lavishly entertained by members of the Medical Faculty of the University of Utrecht. Professor de Josselin de Jong and his staff were particularly gracious and thoughtful in making the meetings a success. O.K.

The Montreal Dermatological Society

This Society met on April 4, 1934, and elected the following officers for two years: *President*, Dr. Albéric Marin; *Secretary*, Dr. Paul Poirier.

Special Correspondence

The London Letter

(From our own Correspondent)

The problem of malnutrition referred to from time to time in these letters has been by no means solved. Under the new Unemployment Act those workers entitled to draw benefit will still receive the admittedly inadequate allowance of 2s. per child per week, but in defence of this it is pointed out that such benefit is only intended for short periods for those who have, at any rate in theory, some other resources in the shape of savings. For those unemployed for longer periods, who by this have automatically ceased to be eligible for benefit, the new Act has brought into existence a new body called the "Unemployment Assistance Board". One of the duties of this body is to provide for the unemployed "according to their needs". Now the agreed statement on basic requirements by the Ministry of Health and the British Medical Association committees on malnutrition laid down standards above those possible on the existing allowances. A distinguished group of

scientists, physicians and physiologists, including the President of the Royal Society, has addressed a strongly worded plea to the press that the term "needs" can only be properly interpreted in consultation with medical and other expert scientific opinion. According to none of the current estimates can the needs of large families be met out of ordinary insurance benefit rates. At least 3s. per child is necessary, for example, but an amendment to insert this in the new Act was defeated in Parliament on the grounds that the new Board was under a definite contract to deal generously with the unemployed, providing not merely a meagre allowance for physical requirements. If this proves to be the case it will be a big advance upon the standards hitherto adopted by the authorities. The provision of school meals and extra milk, for example, without deducting the cost of these from allowances, would go some way to meet the situation. Meanwhile the letter of the scientists remains unanswered, because there is no answer except the carrying out of the assurances given and implied when the Act was under debate.

There still appears to be a difference of opinion about the degree of malnutrition among the child population of the country as a whole. The London County Council's Report for 1933 pays special attention to this point, and claims that a special inquiry made among 10-year-old children showed only 6.5 per cent poorly nourished, a figure comparing very favourably with the results of general medical inspection. The year under review was notable for abundance of sunshine which may possibly have modified to some extent the border-line cases of malnutrition so as to keep them within the standards chosen. The whole point of the matter, however, rests upon such standards, and it is still a debated point as to whether the methods in use have any scientific foundation. Two other minor points appear in the report which warrant remark. There were 170 cases of small-pox during the year, all in unvaccinated children. The second concerns the dietary of boarding schools which came under the Council's care by the Act of 1929. Modifications were made and as a result of these there has been a definite improvement in the health of the children, especially as regards the disappearance of skin infections, an old-standing trouble in the Poor-Law Homes before the Council took them over.

There was a time when no newspaper would ever print the words "venereal disease" and to a lesser extent the beg-bug has suffered from an ill-chosen censorship in polite society. Recently, however, the House of Lords discussed this humble creature as a fundamental housing problem. Not only are the houses in the slum areas infested to an extent of somewhere between 90 and 100 per cent but new houses constructed by local authorities under the various post-war

schemes are said to provide ideal haunts for the parasite. Ceilings and partitions of asbestos sheeting with spaces behind are said to defeat the existing measures of fumigation so far as getting rid of the bugs is concerned. Research on biological and insecticidal lines may reveal some method of dealing with this problem. Meanwhile the bed-bug has been "mentioned" and this is the first step towards getting rid of it.

The great drought continues. After ending 1933 with a rainfall 17 per cent below the average we proceeded to raise this deficit to 26 per cent in the first six months of 1934, nor have things improved much in the last few weeks. In the country districts the shortage has displayed deplorable lack of foresight by the authorities, while in London only the gigantic nature of the enterprise which deals in millions of gallons daily has saved us from severe restrictions. There is a call for a new "Doomsday Book" of England, to assess the water supplies available and their best use. For a country which has devised and supervised irrigation schemes in the driest part of the world this present position is somewhat ludicrous. Fortunately, no direct deleterious effect in health has been so far reported, but indirect effects are difficult to gauge.

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The Edinburgh Letter

(From our own Correspondent)

The annual report of the Department of Health for Scotland, in dealing with the sickness incidence among the insured population, points out that during last year over eighteen million days working time were lost through illness. These figures are based on information taken from all medical certificates received by approved societies operating in Scotland. The total volume of sickness was appreciably greater than in the two preceding years. Incapacitating sickness was found to be more prevalent among women than men, and the figures were higher for married than for single women. Roughly 30 per cent of the total days of increased sickness was due to influenza, but increased incidence from other causes may be linked, it is suggested, with the long continuance of the economic depression. Diseases of the respiratory system were responsible for the greatest amount of incapacity, followed by acute and chronic rheumatic conditions and diseases of the digestive system. The total cost to the funds for all sickness during the year is estimated at £1,815,000. The statistics given, depressing though they may be, do not, of course, indicate that the general health standard of the people is deteriorating; on the contrary there is reason

to believe that the standards of health have risen very considerably in recent times. In these days a more widespread interest is being taken in questions relating to health. By the operation of the National Health Insurance system the working classes have become educated to consult the doctor more freely, and there is an increasing demand in many directions for the extension of the system to include the dependents of insured persons and those of similar economic position.

Professor Clark, in addressing the graduands at the recent graduation ceremony in Edinburgh, referred to the fact that the public was beginning to expect the medical profession to tell them how their physical fitness could be maintained and improved. Certain shallow thinkers he said were never tired of pointing out that the medical profession was endangering its own livelihood whenever it advanced knowledge regarding the prevention and cure of disease. This view was demonstrably untrue, because during the last century the importance and prestige of the medical profession had steadily increased. Referring to the preventive aspect of medicine he said that the prevention and cure of disease at an early stage was becoming recognized as the chief function of the doctor. It was reasonable to hope that this tendency would develop, and one result would be to make the practice of medicine both more difficult and more interesting. It was more interesting to try to enable the human machine to work with full efficiency than to patch up human wreckage so that it could just continue to function. On the other hand, there was no doubt that the diagnosis and treatment of slight deviations from the normal presented problems of exceptional difficulty. This change in the nature of the services demanded from the profession would have the consequence of increasing the importance of treatment because disease would more frequently be seen at an early and curable stage. It seemed probable that in the future medical practice would be very largely concerned with conditions intermediate between the fields covered at present by the sciences of physiology and pathology, and if this conception was correct it followed that an accurate knowledge of the normal functions of the body would become of increasing importance to the medical practitioner.

In my letter last month I described the nature of the evidence regarding medical education submitted by the Scottish Committee of the British Medical Association to the Departmental Committee at present engaged in reviewing the health services of Scotland. In this connection Professor Clark pointed out to the graduands the influence which the rapid development of medical science would exert on the future of medicine. The development of medical science had not been a uniform process, but had consisted of a

relatively short period of intensive advance which had succeeded a long period of stagnation. It had however been their privilege to study medicine during a period of intensive growth, and this privilege had carried with it the penalty of receiving a medical education which had not been a properly thought-out scheme, but merely a makeshift hurriedly adjusted to a rapidly changing body of knowledge. The knowledge which they had acquired was a wasting asset, since unfortunately it would become more and more out of date. The speed with which medical knowledge changed could easily be realized by scanning the text-books used by past generations of students. They had every reason to hope that medical science would make as great advances in the immediate future as it had done in the recent past, and they would therefore have before them the choice of either making a definite effort to keep in touch with future developments, or else of resigning themselves to allow the advance of medical science to pass them by. The danger of the family doctor failing to keep himself abreast of such developments is now well recognized and increased attention is being given to the provision of post-graduate instruction. The present provision is insufficient and inadequate, largely because it does not afford opportunities for the general practitioner to engage in practical work such as would increase his efficiency in the treatment of his patients.

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Topics of Current Interest

A Poliomyelitis Vaccine

The attention devoted in newspapers and current periodicals to experiments now under way in New York for the development of a vaccine against poliomyelitis recalls the fact that such attempts are not wholly new. As early as 1910, Flexner, Lewis and others attempted to develop an immunizing agent of this type. Abramson in 1917, working in the Laboratories of the Department of Health of the City of New York, tested the value of a vaccine prepared from a virus killed by heat according to a method used by Semple for developing a vaccine against rabies. In his experiments, five monkeys each received successive vaccinations with 5 c.c. of a 10 per cent emulsion, each dose of which had been heated to 55 C. for half an hour. Since that time many other investigators have attempted to produce a vaccine that might be established as efficacious, but thus far the results have not proved satisfactory. Now Dr.

Maurice Brodie, working in the Laboratories of the Department of Health of the City of New York, with funds provided by the Rockefeller and other foundations, has developed a vaccine that seems to possess the likelihood of efficacy in the diagnosis and treatment of this disease. Influenced by the earlier work already mentioned and also by the favourable results recently obtained with antigens inactivated by germicides in the prevention of other virus diseases, investigators have attempted to develop a new antigen against poliomyelitis. It was felt that previous workers had not used sufficiently large doses of the antigen and that their tests for immunity were too severe, since convalescent monkeys are only relatively immune.

According to a special communication from Dr. William H. Park, the first experiments with virus inactivated by formaldehyde produced an appreciable immunity in a majority of the animals inoculated. It was found, however, that a concentration of 0.3 per cent solution of formaldehyde was too irritating to the skin; then, with the use of the incubator instead of the icebox temperature, a lower concentration of the germicide was used. With antigens prepared in this way the majority of monkeys inoculated proved resistant to direct intracerebral inoculation of the virus. Moreover, serum obtained from these monkeys possessed neutralizing substances against the virus of poliomyelitis. These antigens rarely produced any irritation of the skin when injected intracutaneously. Using extraordinary precautions, the group in charge of these investigations decided to test out the antigenic properties on themselves before attempting inoculation of children with the antigen. Several members of the research group were injected with a vaccine prepared by adding formaldehyde to a suspension of material from the infected spinal cord. It is proposed, after testing the blood of those who have been inoculated to determine the extent of the immunity developed, to carry the investigations farther, inoculating children against this disease. The vaccine will, of course, have been established as absolutely harmless by the injection into the members of the committee and also as to its efficacy by the studies that have been made on monkeys inoculated with virus following inoculation with the vaccine.

Here is a well controlled scientific experiment in which the safety of all those concerned is guaranteed by modern scientific methods. If successful, it should yield valuable information for the future. It should do much to develop a means for preventing one of the most dreaded of diseases, which strikes fear to the hearts of parents in every community in which it appears.

—*J. Am. M. Ass.*, 1934, 103: 264.

A New Diagnostic Test for Cancer

Laboratory tests with which it is claimed that cancer can be diagnosed are usually performed with the patient's blood. That proposed by Aron* employs the urine, a material which was chosen on the assumption that the abnormal metabolism, or alternatively the degeneration of malignant tissue, should liberate bodies which may be excreted by the kidney. The indicator chosen for demonstrating the presence of these hypothetical bodies is the adrenal gland of the rabbit, the argument here being that this organ is highly susceptible to toxic influences of many kinds. The precipitate obtained when about a litre of urine is treated with alcohol is redissolved and injected into a rabbit in divided doses on several successive days, the animal being killed on the day following the last of these. The "cancer reaction" consists in the partial or complete disappearance of lipoids from the cortex of the adrenal, and was obtained in all but two of a series of cases of malignant disease when a sufficient amount of urine was used for the test; earlier attempts with smaller volumes were not always successful. Control urines from normal individuals, pregnant women, and patients with a variety of other diseases gave negative results. As a diagnostic test it would appear from this information that the procedure is of some service, though one would like to know the extent of the growth which must exist before the test becomes positive: a method which is only reliable in the advanced stages of cancer can be of little value. Since urine is so much more readily obtainable in large amounts than blood, it is perhaps also permissible to suggest that some attempt might be made to fractionate the material obtained from it, with the object not only of concentrating the active substance in it but of gaining some idea of its nature. Some such extension of Aron's observations seems all the more necessary because he goes altogether beyond proposing what is, after all, a purely empirical test. Apparently the serum of a rabbit previously treated with urine from a case of cancer will prevent the cancer reaction in the adrenal of a second rabbit treated with the same urine. This protective effect can also be exerted by the serum of the patient from whom the urine is obtained. These observations, and the (tentative) use of the term "antibody" in connection with them, place the whole matter on an altogether different footing, and it is clearly necessary to inquire further into the basis of these phenomena. An early step which we think should be taken is to study the nature and mechanism of the change in the adrenal cortex, and the possibility of eliciting it with other reagents. There appears to be no reason why any material from a patient suffering from malignant disease should have this particular

* *Presse Méd.*, 1934, 42: 833.

type of effect, and, assuming that Aron's observations can be elucidated in this sense as well as verified, the results might be of interest in directions other than that to which his work owes its origin.—*Brit. M. J.*, 1934, 2: 176.

The Court Expert

Medical men are included within the definition of "expert" in recently issued Rules of the Supreme Court whereby novel provision is made for the services of a "court expert" in non-jury cases. On the application of either side the court will have a discretion to appoint an independent expert to inquire and report upon any question of fact or opinion. If the expert's report is accepted by the parties, there will obviously be a great saving in time and in the laborious preparation of evidence by the witnesses who otherwise must be called by plaintiffs and defendants. It is probable indeed that, if accepted, the report will lead to the rapid settlement of many claims. On the other hand, if the expert's report is not accepted by all parties, it is to be treated as information furnished to the court and is to be given such weight as the court may think fit. This seems to mean that the judge is free to rely upon it to the exclusion of the evidence of the witnesses produced by the parties at the trial. Each side will be entitled to copies of the report and may then apply for leave to cross-examine the court expert thereon. This cross-examination may be ordered to take place either at the trial itself (the court expert being treated as an ordinary witness and being called at such stage of the trial as the judge may direct) or before an examiner. On giving reasonable notice before the trial, either party will be allowed to call one expert witness (or, in exceptional cases and with leave of the court, two or more such witnesses) to deal with the issue referred to, and reported upon by, the court expert. But the parties who thus call expert witnesses will run some risk as regards costs. Even if they win their case they will not be allowed the costs of their expert witness unless the judge specially certifies both that the calling of such witness was reasonable and that his evidence has materially assisted the court in determining the issue. The parties will, however, be allowed the costs of obtaining the advice of their own expert (whether called as a witness at the trial or not) as to whether the action should be brought or defended, or as to whether, or how far, the court expert's report should be accepted, or as to the matters on which the court expert might properly be cross-examined.

The kind of issue in which the court expert's services may be valuable will not necessarily be a medical question. The new rules contemplate the use of court experts on any scientific matter;

recourse may be had not only to medical men but also to engineers, accountants, actuaries, architects, surveyors, and other specially skilled persons. Questions of personal injuries, however, nowadays occupy a large proportion of the total of judicial time; these, and questions involving allegations of negligence in professional treatment, appear to offer occasions for satisfactory recourse to the court expert. It is true that his services are to be limited to non-jury actions, but there seems to be a general drift at present in the direction of eliminating juries if for no better reason than the fact that non-jury actions make smaller demands on judicial time. Be that as it may, the new rules offer an interesting opportunity for the medical profession to play its part in the impartial administration of justice and to remove some of the popular prejudice which the partisanship of expert witnesses has provoked. The scheme is not entirely an innovation; ever since an Act of 1852 the Chancery courts have been able to call on the assistance of experts. Its present application will be experimental; it does not yet extend to the county court. No official provision is made for a panel; the rules merely say that the court expert shall, if possible, be a person agreed between the parties and, in default of agreement, shall be nominated by the court. He is to receive a fee for his report and for any supplementary work required and also a fee per diem for attendance before a judge or examiner. The court will fix the amount of the fees. If the expert thinks any test or experiment necessary, he is to inform the parties and arrange with them as to his expenses and their attendance.

While an advisory committee has recommended this new use of a court expert, the council of the Law Society has found itself unable to approve the idea. The solicitors think it will be hard for "a so-called independent expert" to arrive at a fair conclusion without himself hearing what other experts and witnesses of fact may have to say—in other words he will tend to usurp functions at present exercised by the court. The council also thinks there is a danger of the court expert finding himself to be, and being regarded by the court as, a person who is not merely about to give evidence but as a person whose evidence is about to be acted upon, so that here too the court expert, and not the court, would come to try the case. The Law Society, of course, is the representative body of an extremely conservative profession which has always been able to find objections—often good enough objections, too—to any proposals for shortening and cheapening litigation. The Lord Chancellor's department paid the solicitors the compliment of consulting them about the new rules but was not deterred by their disapprobation.—*The Lancet*, 1934, 2: 145.

Abstracts from Current Literature

Medicine

The Hypertensive Cerebral Attack. McAlpine, D., *Quart. J. Med.*, 1933, 2: 463.

The author believes, with Volhard, that the cerebral symptoms, headache, vomiting, coma and convulsions, formerly attributed to uræmia are due, not to nitrogen retention, but to disturbances of the cerebral circulation, in particular being caused by a further sudden rise in an already high blood pressure. Two main types of hypertensive cerebral attacks are here described: the first, with signs of cerebral œdema, corresponding to what Volhard would call "acute pseudo-uræmia"; the second, without signs of cerebral œdema, corresponding to Volhard's "chronic pseudo-uræmia". The first type occurs usually in persons under 40; the patient may be a child suffering from acute nephritis, or an adult with raised blood pressure, either primary in type or secondary to an old nephritis. The attacks are characterized by the sudden appearance of headache, vomiting, and drowsiness, but rarely coma. There is hypertensive retinitis, with hæmorrhage, exudate and papillœdema. The blood pressure is always high, with a low pulse pressure.

The second type of attack occurs usually in patients between 40 and 65 who have suffered from hypertension for a number of years. The outstanding features are the occurrence of epileptiform seizures; cerebral symptoms, such as headache, transient aphasia or paresis, may previously have occurred. The convulsions may be local or general. Papillœdema is absent, and the cerebrospinal fluid pressure is not raised. The most significant finding is the high blood pressure, and this can usually be shown to have risen above its former high level shortly before the inception of the attack. Usually no organic signs of nervous system involvement remain; sometimes, however, hemiplegic signs of varying degree persist. Apart from the two main syndromes described, certain minor angiospastic symptoms occur—attacks of temporary aphasia, paresis, paræsthesiæ and visual disturbances, lasting for varying periods up to an hour.

The factor common to all the described varieties of cerebral attacks is a raised blood pressure. That a further rise of pressure occurs in each case, precipitating the attack, is difficult to prove, though certain clinical evidence is here submitted in favour of this. In young persons, the cerebral capillaries seem unable to adjust themselves to the rapid rise in pressure and cerebral œdema results. As soon as the cerebral circulation is able to adjust itself to the new conditions, the symptoms subside. Angiospasm may or may not be a factor in this group of cases, (the first type). In middle-aged persons

subject to chronic hypertension the sudden rise in pressure induces spasm of the cerebral vessels with resulting ischæmia. The symptoms depend not only on the degree of spasm but on the site and number of vessels involved. The author admits that there may be other factors than angiospasm concerned in initiating convulsion in these cases, such as biochemical changes in the blood. The prognosis of both forms is good, if there is no accompanying uræmia. If no treatment is initiated death may result, in the œdematous type from medullary compression, and in the convulsive type from exhaustion after repeated seizures. The ultimate prognosis depends on the type of case.

Treatment is directed to lowering the blood pressure, by the speediest means. Liberal venesection may be effective. In the convulsive type, amyl nitrite will often stop the seizures, and should be followed by erythrol tetranitrite every three hours until the pressure begins to fall. In the œdematous type, other modes of treatment will also be necessary, as intravenous injections of hypertonic solutions. Lumbar puncture is effective if judiciously performed.

W. FORD CONNELL

Bundle-branch Block: A case analysis with especial reference to incidence and prognosis. King, J. T., *Am. J. M. Sc.*, 1934, 187: 149.

King has analyzed 155 instances of bundle-branch block in 150 patients at the Johns Hopkins Hospital, 17 of whom came to autopsy. Men constituted 73 per cent of the cases and women 27 per cent. Arteriosclerotic heart disease was the background in 69.5 per cent of cases, syphilis in 9 per cent, and rheumatic infection in 9.7 per cent. In 11.8 per cent the etiological agent was in doubt. The average age of patients showing bundle-branch block as a result of senile breast was about 61 years; of those with syphilitic or rheumatic heart disease 42 years. Previous infections appeared to play no specific part in the etiology of the disease except in the rheumatic group, in which the incidence of tonsillitis and quinsy was relatively high. The disease occurred most frequently among labourers and least frequently among housewives and professional men.

It was found that the various auscultatory phenomena were of less importance in the diagnosis than observation of the surface movements of the cardiac apex. Invariably it was observed that visible and palpable reduplication of the systolic thrust of the apex of the heart indicated a synchronism of the ventricles as a result of a bundle branch lesion.

The electrocardiographic findings were summarized as follows. The P-R interval was prolonged in 28 cases, or 18 per cent. Complete A-V dissociation occurred in 36 cases, auricular fibrillation in 26, and flutter in three. As regards the outcome of the disease, in 104 pa-

tients followed, 76 were reported dead, the average duration of life being one year for the senile group, one year and eight months for the rheumatic cases and less than one year in the syphilitic group.

E. S. MILLS

Anæmia as the Cause of Angina Pectoris in the Presence of Healthy Coronary Arteries and Aorta. Report of a case. Elliot, A. H., *Am. J. M. Sc.*, 1934, 187: 185.

The author reports the coexistence of anæmia and attacks of angina pectoris without disease of the coronary arteries. The patient, a woman of 55, had suffered from a chronic hypochromic anæmia for an indeterminate period of time. This anæmia was associated with a mild hæmorrhagic tendency characterized by epistaxis and purpura. During a period of three years, before her hospitalization, she suffered from severe and frequent attacks of typical angina pectoris. These finally became so severe that a fatal termination was feared. Nitrites gave relief. Examination revealed no evidence of cardiovascular disease other than slight enlargement of the heart. The blood pressure was 100 mm. systolic, 50 mm. diastolic. The electrocardiogram was hardly remarkable. The anæmia was of the order of three million erythrocytes with 5.7 per cent of hæmoglobin. She died of congestive heart failure following an operation for the relief of intestinal obstruction. At necropsy the coronary and other vessels showed no atherosclerosis and the heart muscle was normal for her age. The author explains the angina pectoris on the basis of myocardial ischemia resulting from inadequate coronary flow. The anæmia led to increased cardiac output, which in turn caused cardiac hypertrophy. Under these circumstances the adaptive limit of the coronary flow was overtaxed and angina pectoris resulted.

The author feels that the case demonstrates that angina pectoris may occur in the absence of disease of the coronary arteries, myocardium or aorta.

E. S. MILLS

Congenital Complete Heart Block. Campbell, M. and Suzman, S. S., *Am. Heart J.*, 1934, 9: 304.

The rarity of this condition makes the reporting of these 8 cases and one specimen from the Guy's Hospital Museum of interest. A recent review by Yaters only accepted 30 published cases as congenital heart block. The 8 cases reported were seen over a period of six years. A plea is made for considering congenital heart block in all children with a slow pulse, as in the majority of cases the symptoms are slight. The congenital malformation most often found was a patent interventricular septum. The criteria used in deciding whether heart block was congenital were a slow pulse at an early

age, signs of congenital morbus cordis, the absence of any history of infection, and syncopal attacks in childhood or infancy. All cases were confirmed by electrocardiography. The average heart rate at rest was fifty and in one case a ventricular rate of seventy-five was recorded. Stokes-Adams attacks were found in only a small minority of cases, and usually in the first few years. Other curious abnormalities of the heart were uncommon, the heart usually being enlarged, with marked pulsation and some prominence of the pulmonary arc. The prognosis depends more on the associated abnormalities than upon the heart block. Usually the subject is able to lead an active life with little or no dyspnoea and survives to adult life.

W. H. HATFIELD

Heart Disease from the Point of View of the Public Health. Cohn, A. E. and Lingg, C., *Am. Heart J.*, 1934, 9: 283.

This article is a follow-up study of a preliminary report published in 1926 on the very much-discussed question as to whether or not the death rate from heart disease is increasing. It is shown that before the age of 40 there has been a steady decline in the death rate from heart disease, but that after the age of forty there has been an increase. It is clearly demonstrated that the death rates from infectious diseases have fallen in every decade of life, and as 100 per cent of people must die many persons not now succumbing to infectious disease die of heart disease. If the death rates of heart disease and infectious diseases are added, there is a constant rate over years. It is concluded that the rise in the rate in the circulatory diseases, relatively small though it is, depends largely on the fall in the rate in infectious diseases and that the saving from infectious diseases is due not to saving in the early decades, although this is possible, but due to saving in the latter decades themselves.

W. H. HATFIELD

Surgery

Effects of Diverting the Gastric Contents to the Lower Intestinal Levels. McMaster, P. E., *Arch. Surg.*, 1934, 28: 825.

Though the ulcer-producing effect of the gastric contents on the jejunal mucosa following gastro-jejunostomy is well established, yet little has been made known concerning the effects of diverting the gastric contents to lower intestinal levels. McMaster in his experimental work sought to determine the results of shifting the outlet of the stomach to progressively lower levels from the duodenum to the colon, inclusive, by gastro-duodenostomy, gastro-jejunostomy, gastro-ileostomy and gastro-colostomy. He found that the intestinal mucosa was increasingly more sensitive to gastric juice from the duodenum to

the colon. Jejunal ulceration was noted frequently (45 per cent), while iliac ulceration resulted almost consistently (80 per cent). Hæmorrhagic colitis occurred in a number of animals following gastro-colostomy and secondary anæmia was a sequence. There was a loss of weight and a lowering of the blood chlorides, subsequent to an anastomosis of the stomach to the lower part of the ileum or colon. The acid gastric content was the most important factor in the production of ulceration of the intestinal mucosa near the outlet of the stomach. Loss of weight, where the anastomosis was low down in the ileum or colon, was caused largely by failure of digestion and absorption of food.

G. E. LEARMONTH

Selection of Drainage Material. Spelman, A. E., *Arch. Surg.*, 1934, 28: 837.

Drains into wounds are used to establish an exit for existing unwanted fluid or for that which is expected to form. Varying with the character of the drainage material, almost any will cause a reaction in the surrounding tissues and will influence the efficiency of the drain and the final healing of the wound. Spelman made an experimental study of the effect of rubber tubing and surgical gauze, tacking pieces of these to the parietal peritoneum of animals and recovering them at various intervals. The study was extended to human material when available. He found that rubber tubing delays healing by creating a granulocytic membrane on the wall of the wound where the rubber touches it. An excessive amount of drainage is also induced by over-stimulation of the tissues, with lessened coagulation. In clean wounds it should not be used. In draining infected wounds it may be of advantage. Gauze becomes fixed to the tissues within a few hours. In six to eight days it loosens, but if allowed to remain long past this time it becomes firmly and permanently fixed in the tissues. In clean wounds an ideal surface for rapid healing is left when the gauze is removed. Thombus-formation in vessels is delayed by rubber drainage, while gauze may promote it. Prolonged rubber drainage may cause rupture of blood vessels.

G. E. LEARMONTH

Diathermy and Regeneration of Bone. Weinberg, E. D. and Ward, G. E., *Arch. Surg.*, 1934, 28: 1120.

This is an experimental study. The authors were skeptical when they began this work as to the rise in deep temperature in the tissues, particularly within osseous tissue, which is a poor conductor of electricity, and still more doubtful as to the value of diathermy in delayed union. The microscope demonstrated an increase in formation of new bone when diathermy was used. The experiments performed were for the purpose of determining: (1) whether there is an actual

rise in temperature in bone when an extremity of an experimental animal, is submitted to treatment with diathermy; (2) if there is a rise in temperature of bone, whether this results in any demonstrable physiological effect on bone in normal laboratory animals; (3) whether this physiological effect, if present, hastens repair processes following injury to the bone.

Briefly summarized the deductions made were that: (1) the temperature is raised in the bones and muscles when diathermy is properly applied; (2) the local circulation is increased by the rise in temperature; (3) the formation of new bone is accelerated by this increased physiological activity.

G. E. LEARMONTH

Obstetrics and Gynæcology

Fetal Mortality in Contracted Pelvis with Prolonged Labour and Delivery through the Birth Canal. Peckham, C. H. and Kuder, K., *Am. J. Obst. & Gyn.*, 1934, 27: 537.

The gross fetal mortality attendant on delivery through the birth canal following prolonged labour in cases of contracted pelvis was 19.23 per cent in a series of 442 cases, and even after correction for unrelated causes was 13.56 per cent. An increased death rate was observed among black women, and it was definitely higher in multiparæ than in primiparæ. The highest mortality was seen in cases of flat pelvis, and the lowest in the generally-contracted variety, with the rachitic group falling between the two. Almost half the labours had to be terminated by some form of operative means, and there were 24 instances of craniotomy. The mortality rate was satisfactory if spontaneous delivery occurred, but with operative procedures was 27.17 per cent, even after correction. Breech extraction and podalic version were extremely lethal to the child. Children born to women with flat pelvises were about average in size, but were several ounces below normal if the pelvis was generally contracted or rachitic. The fetal mortality varied directly with the size of the child.

The wisdom of allowing a test of labour to progress more than twenty-four hours, providing uterine contractions are adequate, is dubious, unless all signs point to speedy and spontaneous termination. Low cervical Cæsarean section at that time becomes the procedure of choice for the child, although probably entailing some added risk to the mother.

ROSS MITCHELL

Placenta Prævia. Wilson, R. A., *Am. J. Obst. & Gyn.*, 1934, 27: 713.

During a period of eight years and eight months ending September 1, 1933, 102 cases of placenta prævia were treated in the Methodist Episcopal Hospital, Brooklyn. In this number

68 were partial and 34 complete, marginal cases not being included. There were 2 maternal deaths, giving a percentage of 1.96. Conservative methods were used in 70 cases, with 2 maternal deaths and 28 viable stillbirths. The 32 cases treated by classical Cæsarean section, however, resulted in no maternal deaths or stillbirths. Transfusion was performed once or more in 15 patients, or in 14.7 per cent of the cases.

In view of recently published statistics and his own results, Wilson recommends Cæsarean section in most cases of partial and complete placenta prævia. The patient should be in a good hospital and in the hands of a competent operator; poor results may be expected if these two requirements are not fulfilled. It is imperative that blood be quickly available for transfusion before, during, and after operation. If the patient must be treated at home, conservative methods are followed. This would apply also if the patient were infected, or the cervix fully dilated and delivery imminent. Excessive hæmorrhage at the time of operation may be controlled by packing the uterus with gauze soaked in mercurochrome. Cæsarean section not only gives maternal results as good as, or better than, the conservative methods, but in addition we need no longer completely disregard the baby, thereby saving many which would otherwise be lost.

ROSS MITCHELL

Dilaudid-Scopolamine in Obstetrics. Ruch, W. A., *Am. J. Obst. & Gyn.*, 1934, 27: 717.

Dilaudid, 1/32 gr., used with 1/120 grain of scopolamine, produces a satisfactory seminaresis for women in labour. In this study, 101 cases of dilaudid-scopolamine analgesia were compared with a series of 100 cases to which morphine-scopolamine had been given. Eighty per cent of those receiving the dilaudid combination showed signs of narcosis within ten minutes, and when twenty minutes had elapsed all but one patient were affected; with the morphine combination only two patients noted any effect in ten minutes, and 15 per cent required thirty minutes or longer.

Dilaudid did not cause any appreciable diminution in uterine contractions, and in fact, contractions seemed to be better after relaxation by the drug. Nausea occurred almost three times more frequently with morphine than with dilaudid. Infantile asphyxia occurred infrequently—twice in clinic cases and not at all in private cases. After-pains were relieved effectively by the use of rectal suppositories, each containing 1/24th grain of dilaudid.

Pædiatrics

Cases of Median Nerve Palsy produced by Attempted Intravenous Injections of Calcium Chloride. Stevens, H., *Brit. J. Child. Dis.*, 1934, 31: 117.

Drugs are nowadays frequently introduced into the body by the intravenous route. The vessels crossing the antecubital region are commonly utilized for this purpose on account of their accessibility. Solutions of the salts of arsenic, antimony, lead, gold, and calcium, among others, are in daily use. Any of these solutions, escaping into the perivascular tissues in sufficient concentration can cause a local, painful reaction. Sloughs may form which are slow in separating and healing.

The author records 3 cases in which calcium chloride in 10 per cent solution was injected intravenously with untoward results. In the first case, a girl of 13½ years, five injections of 5 c.c. were given *via* the left median basilic vein on alternate days, and were followed by complete motor palsy of the region supplied by the median nerve and by complete anæsthesia of that part supplied by its left palmar branch. In a man aged 34 one intravenous injection of 5 c.c. into the left median basilic vein was followed by pain and severe tingling in the thumb and first two fingers of the corresponding hand, which spread up the wrist. The following day the patient was unable to flex the distal phalanges of the first three digits, with defective rotation of the thumb and loss of the power of pronation in the forearm. Death occurred from sepsis following a chest condition (tuberculosis). Post-mortem examination showed an organized thrombus in the basilic vein, and scar-tissue surrounding the median vein proximal to the bend of the elbow. The third patient was a man, aged 46. One injection of 10 c.c. was given him into the left median cephalic vein, with amelioration of his condition. Ten days later 15 c.c. were injected into the right median basilic vein. The next day sensibility to pain and touch was absent in the distribution of the lateral palmar branch of the median nerve, and there was some deficiency of the medial cutaneous nerve of the forearm. Eventually, a slough formed on the medial side of the cubital fossa which gradually healed, but the neurological signs persisted.

For anatomical reasons, which the author details, it is best to choose the median cephalic vein or the cephalic vein itself for the purpose of intravenous injection. The worst neurological complication which can ensue then is paresis of the lateral cutaneous vein of the forearm, which is a trifling matter. It would be well also to consider whether more dilute solutions could be used, with satisfactory results.

JOHN NICHOLLS

Vitamin A Deficiency in Children. Mackay, H. M. M., *Arch. Dis. in Child.*, 1934, 9: 133.

The author carried out a series of tests over 22 months, seeking evidence concerning the existence of a possible deficiency of vitamin A in London babies getting a liberal allowance of milk and later "table food" in addition, and on the effect on their health should such deficiency exist.

All the children were fed on a roller-process dried milk containing iron and ammonium citrate, to which were added vitamin D, orange juice and sugar. From the age of 7 or 8 months solid food, including eggs, fish, meat and vegetables, replaced part of the milk ration. Approximately half of the children (60) received extra vitamin A. The other half were used as controls. The following results were obtained.

1. Slight vitamin A deficiency existed in the control group, and hence is probably of common occurrence in artificially-fed infants in England, unless this vitamin is specifically added to their diet by the administration of cod liver oil or some other potent source of vitamin A.

2. The effect of this slight vitamin A deficiency is apparently to diminish resistance to infections of the skin, such as occur with sore buttocks, intertrigo, and dribbling rashes, this susceptibility preceding the obvious clinical changes in the skin noted by many observers.

3. Diminished resistance to general infections was not among the first effects of slight vitamin A deficiency in infants, and a large excess of vitamin A does not raise the general resistance.

4. Diminished growth is not among the first effects of vitamin A deficiency in infants.

JOHN NICHOLLS

Oto-Rhino-Laryngology

On the Function of the Saccule. Asheroft, D. W. and Hallpike, C. S., *J. Laryn. & Otol.*, 1934, 49: 450.

Experimental work carried out on the frog shows certain positive evidence concerning the function of the saccule. The saccule can no longer be considered a position-sense receptor. Action currents were recorded in the saccular nerve of the frog, employing a micro-manipulative technique in combination with a conventional amplifying system and a cathode ray oscillograph. These action currents occurred in response to vibrational stimuli, the frequency of the stimulus being reproduced accurately up to a frequency of at least 500 per second. From these experiments it is concluded that the saccule in the frog is an organ of vibration sense and that in man the saccule is concerned in the reception of bone-conducted sounds. The implications of this possibility are widespread. The actual physiology of hearing may not be entirely a matter of resonance perception by the basilar

membrane, but also a question of frequency reproduction of the note heard by the saccule. Clinically, it is suggested that since both the saccule and cochlea perceive sounds separately, the measurement of bone conduction by the usual tests is not a measure of cochlear sensibility.

GUY H. FISK

Therapeutics

The Treatment of Cardiac Cases. Cassidy, M. A., *Brit. M. J.*, 1934, 1: 45.

Of 843 cardiac cases seen in private practice by the author, no less than 29.5 per cent were labelled "neuropathic"; of the remaining 591 organic cardiac cases, only 5.6 per cent were seen because of rheumatic valvular disease. A huge majority are classed as "degenerative", 31.3 per cent hypertensive, and the same percentage, decreascent arteriosclerosis. It is obvious that valvular heart disease occupies too important a place in the minds of many physicians.

Most cardiac patients are treated with an excess of caution; they suffer from too much rest and restriction of activities. Prolonged rest is certainly essential in acute heart infections, especially rheumatic or diphtheritic; nor should violent exercise be permitted too soon after either tonsillitis or influenza.

"The schoolboy's heart" is discussed at some length. The cases are common and difficult to deal with. The patient is usually a delicate child with a systolic murmur, who has been labelled cardiac, and now has all the features of "the effort syndrome". The author always allows games under supervision in these cases, and never has found any harm resulting.

The treatment of all cardiac neurosis may be summed up in one word—reassurance. If after careful investigation, clinical, electrocardiographic, and x-ray if possible, we find nothing amiss, we must assure the patient with no reservations that there is nothing whatever the matter with the heart, and that no restrictions of any sort are necessary. Sometimes a short course of bromide or luminal is helpful, and sometimes return to full activity must be graded. Digitalis is contraindicated.

Even in organic heart disease the psychic aspect is important. Associated with any organic condition there may be a considerable anxiety state, and all the symptoms sometimes found in cases of, say, mitral stenosis, may be of psychological origin.

It is commonly assumed that all organic heart disease must produce symptoms and require treatment; this is of course not true. Valvular disease is often compatible with a normal quiet life, so long as the individual is fortunate enough to be unaware of its existence. The army was very productive of symptom-filled valvular cases.

When valvular disease is discovered we must

determine to what extent, if any, the heart's efficiency as a pump has been impaired, and whether indeed any of the symptoms complained of are due to the organic lesion or to an added anxiety state. Particular inquiry must be made into dyspnoea on exertion, with the degree of effort required to induce it, and whether the patient is able to sleep flat in bed without nocturnal dyspnoea or wheezing. Early signs of congestive failure must be looked for. Often after a negative examination we can assure our patients that their valvular lesion is no serious disability and is compatible with many years of average health. Advice regarding moderation in exercise and consumption of food, alcohol and tobacco should be given.

W. FORD CONNELL

The Prevention and Treatment of Individual Attacks of Angina Pectoris. Evans, W. and Hoyle, C., *Quart. J. Med.*, 1934, 3: 105.

The authors have previously shown that of 16 drugs in common use in the continuous drug treatment of angina pectoris, none lessened the frequency or severity of attacks. They now present the results of a three-years' research on a series of 122 patients with angina pectoris, paying particular attention to the comparative value of vasodilator drugs for the *immediate* treatment and *prevention* of attacks. Syphilis was present in 25 of the series. The cases were observed in the Cardiac Department of the London Hospital, each patient attending fortnightly and being required to make strict report of his condition between visits. The following drugs were tried: glyceryl trinitrate (trinitrin) in tablets, in 1 per cent alcoholic solution, in solution in oil, and also as proprietary preparations (three); also amyl nitrite, sodium nitrite, brandy, chloroform, carminatives, and hypnotics. It was concluded that glyceryl trinitrate in tablet form, when allowed to be absorbed from the mouth, is by far the most effective agent for relieving attacks and for their immediate prevention (the tablet being taken immediately before exertion such as would ordinarily cause pain). The tablets were found to deteriorate rapidly when exposed to light and air, so it is recommended that they be always dispensed in a screw-capped or waxed cork bottle, and used within two months of manufacture. The authors feel that these tablets should undoubtedly hold first place in the routine treatment of angina, for they are not only most effective but are also the cheapest and most convenient remedy. The tablets are best made up with a lactose base—when they will then dissolve readily on the tongue; tablets with a chocolate base are also good, but must be chewed and then allowed to be absorbed from the mouth (never swallowed). Amyl nitrite was disappointing, and is only recommended for the rare cases which glyceryl trinitrate fails to relieve. It has

the disadvantage of being useless for the prevention of attacks.

From their observations, the authors conclude that the use of glyceryl trinitrate tablets immediately before expected anginal attacks is a safe means of preventing pain, and should be used far more widely in routine treatment than it is at present. If by taking the tablets judiciously the patient is enabled to carry on at his occupation or to lead a fuller life with comfort he should be encouraged to do so in most cases, instead of insisting on the rest and inactivity which has always been thought so imperative. The use of the tablets at fixed intervals was found to be far less satisfactory than when the patients were allowed to take the drug at their own discretion, before periods of exertion. In no case were deleterious effects observed, even after two or three years of free use of the drug.

W. FORD CONNELL

Pathology and Experimental Medicine

Congenital Urethral Valves in New-born Twins. Borovsky, M. P., *Am. J. Dis. Child.*, 1934, 47: 455.

The twins, identical males, were the result of the 8th pregnancy. Both had undescended testes. One developed oedema of the abdomen on the fifth, the other on the seventh day. Examination of the urine in both showed it to be normal. The temperature rose to 101 and to 100.4° in the twins on the 11th and 12th days, respectively. Albumin and pus were found in both urines. The oedema continued to spread, involving the face and hands; the bladders were much distended and required catheterization which was accomplished without difficulty. One child died on the 16th, the other on the 17th day. Autopsy revealed urethral valves of a one-way type at the base of the bladder in both twins, hypertrophied bladders, and degenerating kidneys. This account is of importance in showing that these defects in structure usually attributed to some mechanism other than a defective heredity are in reality due to defective inheritance, since both twins, which in this case were developed from a single fertilized egg and so had identical hereditary patterns, also showed identical malformations in the undescended testes and urethral valves.

MADGE THURLOW MACKLIN

On Abnormal Course of the Pulmonary Veins. Munck, W., *Acta Path. et Microbiol. Scand.*, 1933, 10: 321.

This is a description of the autopsy findings in a boy who died at almost 3 months, suddenly, as a result of the rare malformation exhibited. The pulmonary veins did not enter the left atrium, but united into a single trunk which penetrated the diaphragm through the hiatus

oesophagei and opened into the portal vein. Thus all the blood from the lungs followed an anomalous "lesser circulation" route through the liver and around to the right heart; and the infant would have been still-born had it not been that both foramen ovale and ductus arteriosus were patent, the latter being larger than a lead pencil. Through these surviving fetal openings blood (largely venous, it is true) was admitted to the systemic circulatory system. As might be expected, the right heart chambers were much enlarged, the thickness of the right ventricle being almost one centimetre. The left heart, on the other hand, was of comparatively delicate structure, and this may be said also of the aorta up to the point of entrance of the ductus arteriosus. A clinical history was not obtained. The weight was 4,100 grams.

Reports of a number of similar cases are presented from the literature, one of which (Arnold) lived for fifteen months. The anomaly is attributed to some interference with the early capillary connection of the sinus region of the young heart, and a deflection of the blood outflow from the pulmonic region along lines of least resistance through the capillary plexus bordering the primitive intestine to the liver region. This channel gradually developed into the extended pulmonary vein described.

It seems quite probable that malformations of the pulmonary veins of serious type such as this are a much more frequent cause of early death in infants than is realized.

C. C. MACKLIN

Vitamins A and D: Their Relation to Growth.

Sutherland, R., *Brit. M. J.*, 1934, 1: 791.

The results of a dietary investigation of 575 school children of the poorest classes, taking grossly deficient diets, are given. The author administered to half this group a concentrate of vitamins A and D in an amount equivalent to more than one ounce of high grade cod liver oil, daily, for six months, while the control group received similar but inert capsules. He found little if any difference either in the rate of growth or in susceptibility to infection, in the two groups. He concludes that the vitamin concentrates corrected only one dietary deficiency, leaving uncorrected associated deficiencies of equally essential dietary constituents. A well balanced dietary, then, is very important—a milk supplement being distinctly more valuable than a direct supplement of vitamins A and D.

W. FORD CONNELL

Radiology and Physical Therapy

Common Misconceptions Concerning Massage and Mechano-Therapeutics. Cyriax, E., *Brit. J. Physical Med.*, 1933, 8: 92.

Surrounding the treatment of disease by active and passive movements there are many erroneous

views. Not only are nomenclatures, as used, extremely faulty, but many misconceptions also obtain in relation to the active application of this art. Some of these erroneous views are due to the fact that many who have written on the subject have quite an insufficient knowledge of the subject. A very common misconception is that a period of rest should follow every massage treatment. This is quite without physiological basis, for both clinical and experimental evidence shows nothing whatever in the nature of a strain or severe reaction for which rest is essential in order to ensure recovery.

In prescribing muscle massage, most medical men have in mind stimulating the venous and lymphatic return. While this may be applicable in situations where there is stasis and œdema, it is not true in muscles that are weakened because of disuse or nerve impairment. Because of experimental researches we now definitely know that massage influences muscles by stimulating their nervous elements. Since effleurage, so frequently employed, can produce no stimulatory effect, it is little to be wondered at that the treatment of infantile paralysis and other muscle dystrophies is often very slow in showing any improvement. Since many are central in origin re-education is the indication that should chiefly be served.

Many still consider that massage of the colon has for its object onward propulsion of colonic contents. When we recall the true picture of the colon as revealed by the x-ray, it is obvious that onward propulsion does not explain the results obtained. It is not the direction of the massage but energetically applied massage that stimulates the nerves and non-striped muscle and thereby increases their power, thus enabling them by their own efforts to promote onward movement of their contents. In muscle contractions one commonly sees massage of the affected group followed by stretching. The sum-total of this procedure is to increase the power of the affected muscle, which tends to increase the disability. Correctly applied, the antagonistic muscles should be developed by energetic massage and resisted exercise. In the case of scoliosis it is the elongated muscles that should be massaged and further developed by resisted exercise. Manual vibrations, commonly stated as being extremely tiring to produce, since the muscles of the operator's entire arm are placed in a state of powerful complete tetanus, are correctly executed by a small amount of contraction and relaxation of the muscles of the operator's forearm.

E. E. SHEPLEY

Graduated Muscle Contraction, Its Rationale and Technique. Smart, M., *Brit. J. Physical Med.*, 1933, 8: 87.

To physiologically sustain tissues, a healthy state of arterial, venous and lymphatic circula-

tion is essential. In damaged tissues this function is even more necessary. Muscle contractions and relaxations are a powerful means of promoting and maintaining this situation in both the muscles and the adjoining tissues. To prevent the formation of adhesions which so constantly follow reparative changes it is necessary to eliminate interstitial oedema and the organization of inflammatory exudate. While effusion into tissues is necessary to repair and is beneficial, it must be transitory and never permitted to stagnate. Not only is the organization of effusion to be feared, but its persistence interferes, because of pressure on nutritional channels, with normal local metabolism and starvation results.

Properly instituted, muscle stimulation functions not only in dissipating oedema in the involved area but it also prevents the formation of adhesions between muscle fibres, between tendons and their sheaths, and also between joint surfaces. In addition, nutrition and absorption is stimulated, waste products are more quickly removed, muscle tone is maintained, and muscle wastage is prevented.

The basis of this method is the antithesis of rest. In other words it is a form of painless intensive exercise that is graded according to the circumstances of the case. No matter how painful a joint may be after injury, the muscles controlling the joint can be painlessly contracted and relaxed, and in this way not only is rapid repair stimulated but early extensive movement of the joint is facilitated. Since the object of the treatment is to assist natural repair, early treatment is indicated and, thereby, late effects which are the common cause of pain and disability will be prevented. Constant personal control of the degree and rate of stimulation is essential in order to obtain a type of response that will not produce harmful effects.

E. E. SHEPLEY

The Radiology of Heart Disease. Parkinson, J., *Brit. M. J.*, 1933, 2: 591.

The examination of a patient with doubtful or serious heart disease is incomplete unless it includes radiological examination. The protean individuality of the cardiovascular shadow is what strikes one on routine examination. No two radiograms of the heart are exactly alike. Anterior films of the heart alone are often inadequate. One or both oblique positions should also be utilized. Visualization of the oesophagus by barium paste is also often of aid in diagnosis. The difficulties surrounding the radiology of heart disease largely disappear if, instead of looking for general enlargement, attention is centred upon the particular chambers or great vessels which may be modified in size. The

cardio-thoracic ratio is, however, a useful measurement which will probably come into general use (this is a comparison of the transverse diameter of the heart with that of the thorax).

The author warns against diagnosing cardiac enlargement without adequate cause. He has been struck by the frequency with which a condition of slight scoliosis can so distort the heart shadow that enlargement is simulated. Twisting the patient a little to one side, usually the right, will correct this distortion.

It is now recognized that x-ray examination will often reveal the full picture of mitral stenosis when its presence has not even been suspected clinically. After the characteristic murmur, the particular enlargement of the right auricle, so well seen in the right oblique position, is the surest sign of this condition. In aortic incompetence, enlargement of the left ventricle is the conspicuous feature. Pericarditis with effusion is well-studied by x-rays. Congenital malformations are now understood better than ever before, thanks partly to radiology, which so well distinguishes congenital from rheumatic heart disease in children. Unexpected pulmonary disease, intrathoracic tumour, or goitre, will at times be discovered during the routine examination of heart cases. It is noted that myocardial disease *per se* has no distinctive effect on the cardiac outline. If great enlargement be found in this condition, hypertension is always co-existent.

W. FORD CONNELL

Lobar Atelectasis as a Cause of Triangular Shadows in Bronchiectasis. Warner, W. P. and Graham, O., *Arch. Int. Med.*, 1933, 52: 888.

The authors report the occurrence of triangular basal shadows in chest roentgenograms in 6 per cent of all cases of bronchiectasis. They believe their presence is diagnostic of bronchiectasis, and when noted the diagnosis should be confirmed by lipiodol injections. These triangular shadows are caused in some cases at least, and probably in all cases initially, by a lobar atelectasis of the bronchiectatic lobe. The atelectasis, they believe, is due to the plugging of the terminal bronchioles by the swelling of the bronchial wall with an inflammatory exudate. Among their cases they cite one in which the left lower lobe was represented by a triangular shadow, and when removed surgically showed the lobe completely collapsed and the bronchi were thick-walled and dilated. They produced triangular basal shadows experimentally in dogs by completely occluding the bronchi of the lower lobes. If the animal was killed an atelectatic lobe was found situated in the thorax in such a position that it undoubtedly caused the shadow. If on the other hand, the obstruction

were removed, the lobe was seen to expand and the triangular shadow disappeared. Atelectatic bronchiectatic lobes may occasionally be found on physical examination, and they regard such physical findings as diagnostic of bronchiectasis.

LEYLAND J. ADAMS

The Fate of Fibromyoma of the Uterus after Radiotherapy. Carscaden, J., *Am. J. Roentgenol. & Rad. Ther.*, 1933, 29: 511.

The author believes that the conventional teaching "that fibromyomas larger than a three months' pregnancy should be removed", is not based on a comprehensive review of a large number of cases treated. The author has followed a large group of cases treated by radiotherapy over an average period of seven years (one to eighteen), and the study showed: (1) in no case was the tumour increased in size; (2) in 8 cases the tumour was practically unchanged; (3) in 104 cases the reduction was satisfactory. In 71 of these 104 the uterus returned to normal size; (4) in 26 cases the mass decreased to one-fourth the original size, and in 7 cases to one-half the original size. In 63.4 per cent of the cases there was complete shrinkage of the tumour mass. In only 2.6 per cent was there no reduction. In an average period of seven years no serious degenerative changes were observed. Following a sterilizing dose a satisfactory shrinkage can be promised in 90 per cent of all cases treated.

E. E. SHEPLEY

Anæsthesia

Divinyl Oxide Anæsthesia in Obstetrics. Bourne, W., *The Lancet*, 1934, 2: 566.

The rapidity with which the state of anæsthesia may be reached when divinyl oxide is inhaled, the promptness of recovery and the relative safety suggested its probable usefulness in obstetrics. The following analysis is based upon its administration to 50 parturient women. The technique in 34 cases consisted of bubbling oxygen through divinyl oxide at the rate of 700 c.c. per minute in a closed system with a carbon dioxide absorption attachment. Fourteen patients received the divinyl oxide by means of the "open mask", while the remaining 2 were given a mixture of nitrous oxide, divinyl oxide and oxygen. The operations were classified as follows: 39 spontaneous deliveries in which 32 episiotomies were performed; 1 high forceps; 5 mid-forceps; 2 low forceps; 1 bag induction; 1 Cæsarian section with sterilization; and 1 low Cæsarian section. The rapidity of induction is very striking; a few inhalations being sufficient. There is little excitement, any desired degree of relaxation can be obtained, and recovery is very rapid. Respiration is not interfered with as

much as when ether is employed, and what little circulatory depression does occur compares favourably with that occurring when ether is given. Post-anæsthetic nausea and vomiting are no more frequent than is usual in obstetrics.

Previous investigators have shown from the determination of the concentration in the blood necessary to produce anæsthesia that the anæsthetic potency of divinyl oxide is four times that of ether (diethyl oxide) and greater than chloroform as one and three-tenths is to one. The author carried out several investigations to determine the effect of the anæsthetic on liver function, employing the bromsulphalein dye test. It was shown that the administration of divinyl oxide is followed with but slight dye retention and consequently practically no liver damage. Since the compilation of the above data from 50 cases, 102 more have been treated with similarly successful results, and it is felt by the author that divinyl oxide is a very suitable agent for employment in obstetrics, as it possesses all the above-mentioned desirable features along with that of minimal danger to mother and child. It is recommended that the anæsthetic be administered with oxygen, but it may be given alone with relative safety.

ARTHUR WILKINSON

Hygiene and Public Health

Sericite in Foundry Dust. Hurlburt, C. S., Jr. and Beyer, D. S., *J. Ind. Hyg.*, 1934, 16: 169.

W. R. Jones, in England, has recently advanced the theory that fibrous minerals, notably sericite, are the chief cause of silicosis rather than free silica. He states that in the insoluble residues of silicotic lungs sericite particles predominate over quartz, that gold-bearing quartz in South Africa has a small percentage of sericite while that of India has none, and he accounts for the high incidence of silicosis in South Africa and the low incidence in India by this fact.

Hurlburt and Beyer made an examination of the dust of two foundries, in one of which a high incidence of silicosis had been reported, whereas no claims had occurred in the other. The foundries were comparable in size, operations, number of employees, age of employees and length of service of employees. Dust counts revealed a somewhat dustier condition in foundry B (where no claims for silicosis had occurred) than in foundry A. The petrographic analysis of the sand used in the two foundries indicated a similarity, except in the case of one fine sand used for facing in foundry A. This sand had a high sericite content. Actually sericite constituted numerically more than 60 per cent of the particles less than 10 microns in diameter.

F. G. PEDLEY

Obituaries

Dr. Arthur Percival Procter, Chief Medical Officer in Vancouver for the Canadian Pacific Railway, died in the General Hospital, Vancouver, on August 20, 1934, as a result of a bullet wound inflicted on August 3rd by T. A. Sargood, of Revelstoke, a former C.P.R. engineer. The shooting occurred in the C.P.R. station about 12.30 noon, as Dr. Procter walked into his office. Sargood, who had waited for him for about half an hour, jerked the revolver from his pocket and fired. His first bullet struck the doctor. He fired again, but the bullet missed and crashed through the office door. The physician suffered a 45-calibre revolver wound through the lower chest. For some time his medical attendants held out hope for his recovery, as he had shown improvement for some time. Later, however, the hospital authorities realized that he was not making the progress that had been expected.

With the passing of Doctor Procter, Vancouver loses one of its most prominent and most respected medical practitioners. He was born in Ashfield House,



Arthur Percival Procter

Macclesfield, Cheshire, on July 28, 1867. He came to Canada in 1886 and studied medicine at McGill University. Affected by lung trouble, he was ordered to a drier climate, and finished his medical course at Manitoba University, where he graduated with the degree of M.D.

Dr. Procter was first identified with the Canadian Pacific Railway at Donald, B.C., in 1896, the year of his graduation. He went to Kamloops in 1898, and to Vancouver in 1905. In 1909 he became Chief Medical Officer of the C.P.R. for British Columbia, a position which he held ever since, with the exception of the years he served overseas during the war.

Doctor Procter took a leading part in the organization of Tranquille Sanatorium at Kamloops, and since 1912 had been registrar of the College of Physicians and Surgeons for British Columbia. For seventeen years, he had been Chief Medical Officer at Shaughnessy Military Hospital. One of Doctor Procter's last public activities was to journey to Port Alberni, Vancouver Island and help in presentation of a testimonial to a school principal who had taught there forty-nine years. Doctor Procter himself had been his predecessor at the Port Alberni school in 1889.

Doctor Procter leaves a family of five, his wife,

one son, Dr. A. P. Procter, Jr., and three daughters, Mrs. Geoffrey Gowland in England, Mrs. R. Carr-Harris, and Anne, at home.

AN APPRECIATION

The writer first met Doctor Procter in Nanaimo in 1894 when he called to obtain some advice concerning University affairs, and since then, for forty years, we have kept in touch. As the years went on we became more intimate, and since his settling in Vancouver, twenty-nine years ago, our friendship has deepened with the passing years. I ever found him a true and loyal friend living up to the ethics of his profession and the higher ethics of a Christian. His record of service embraced many activities and the positions he occupied proved his worth and the respect in which he was held. For twenty-five years he was Chief Medical Officer of the Canadian Pacific Railway for the British Columbia Division. For twenty-two years he was Registrar of the College of Physicians and Surgeons here, and for seventeen years he was Chief Medical Officer at Shaughnessy Military Hospital. This record of service is unique and proves not only the esteem in which he was held but also his capacity as an administrator.

In his railway and military work he had many trying problems to solve, in which truth and justice had to be maintained, and in which not always could he please by his decisions the parties involved. But, knowing the character of the man, I am sure they were always treated with understanding, with fairness and sympathy. Tact was needed in much of his work and he was abundantly provided with that valuable resource. In his twenty-two years of service to our profession his work was carried on smoothly, without friction and in the best interests of the profession. His sympathetic nature will long be remembered by many of our members, newly coming to the province, for he was always ready with advice and wise counsel and a sympathetic understanding.

As a friend he was a friend indeed, as is evinced by the multitude of friends he has left behind. And as a man, he was a Christian gentleman. His many years of service as people's and as rector's warden only prove further the esteem and respect in which he was held and the abundance of the service he was giving. I cannot close without quoting from a letter received by Mrs. Procter from an old friend of the Doctor's, one who had known him from the time of his first year in practice, when he was stationed at Donald in the C.P.R. service in 1896. This friend, himself a cleric, had kept in close friendship with him all these thirty-eight years, and he says: "He was a lover of all that is good and noble and the deep religious convictions he had received from his mother followed him through life. . . . He had the unfailing cheerfulness of a good conscience, and no one who knew him well could fail to admire and love him. I was never with him without experiencing the happiness that comes from the friendship of a truly good and upright man."

He was my friend, too, and I and his many other friends bid him farewell with deep regret.

R. E. McKECHNIE, (from the *Bull. Vancouver Med. Ass.*, 1934, 10: 226).

Dr. Thomas Lowell Butters. In the death of Dr. Thomas Lowell Butters, Vancouver has lost one of its most outstanding general practitioners, and the medical profession one who stood very high in the affections of his medical confrères. After an illness of six months' duration he passed away at the Vancouver General Hospital on August 11, 1934, at the age of forty-four.

Of United Empire Loyalist stock, he graduated in medicine from Toronto University in 1913 and was one of the first to proceed overseas, serving with the No. 1 Canadian General Hospital at Etaples, then as medical officer of the 27th Battalion, later as adjutant of the Canadian Convalescent Home at Epsom. He returned to Canada in 1918. He was in charge of occupational therapy and was D.A.D.M.S. in Toronto. He attained his majority and was a recipient of the 1914-15 Star. On demobilization Dr. Butters practised at Courtenay, Vancouver Island, until 1926. He removed to Vancouver where, due to his capability, zeal and personality, he soon had a large and growing practice and in 1928 was appointed to the Vancouver General Hospital staff.

His was a pleasing personality. Wherever he went he was regarded with affection. Everyone with whom he came into contact had a good word for him. He had hosts of friends in every walk of life. In his work he disregarded himself entirely, giving his best efforts to the interest of his patients at all times. They idolized him. As a member of the Medical Association he worked hard on any committee to which he was appointed, and was particularly successful as a member of the Summer School Committee in 1932. Among his intimate friends he was always a favourite. "There was only one Tommy Butters", staunch and reliable under any circumstances.

Doctor Butters married in London, England, in 1915, Helen, daughter of Dr. and Mrs. W. A. Richardson, of Victoria. He leaves his widow and three children, Thomas, Elizabeth and Dennis.

We have lost a friend.

A.L.

Dr. Edward Worthington Connolly, of Vancouver, suffered a cardiac attack while at work on August 28th. He unfortunately resumed his activities on August 30th, and was carried off by a second seizure. Dr. Connolly, who graduated at Queen's in 1900, was sixty when he died. He served overseas with the C.A.M.C., first at the Dardenelles, and later in England. He had practised in British Columbia since 1903, first in the interior, and, since the war, in Vancouver. Dr. A. K. Connolly, of Victoria, who is a brother, and his widow and son, survive.

Dr. Jean Baptiste Delisle, formerly of Ottawa, Ont., died after a long illness in Notre Dame Hospital, Montreal, on August 11, 1934, at the age of 72 years.

Dr. Delisle was born at Cap-Santé, Que., and was a graduate of Laval University, Quebec (1892). He settled in practice at Montreal. His wife was Miss Anna Senécal and she predeceased him nine years ago. Dr. Delisle is survived by two sons, André and Rosaire; and two daughters, Théophanie and Berthe.

Dr. Charles Elias Frain, of Haliburton, Ont., aged 40 years, was drowned on August 14, 1934, in shallow water at Kushog Lake. He had motored to Wag-a-nog Inn, and went in bathing with a number of tourists. On his first dip he took in a mouthful of water, and returned to a diving-board, where he rested. When he next took a short swim, he sank and failed to come up. His body was recovered after five minutes, but life was extinct. Dr. Speck, of Haliburton, said death was due to heart failure, as there was very little water in the lungs. Dr. Crowe, Coroner of Minden, deemed an inquest unnecessary. Dr. Frain, whose home was in Toronto, settled in Haliburton eight years ago. He is survived by his widow and one son. He was a graduate of the University of Toronto in 1916.

Dr. Thomas Lovett, of Montreal, died at St. Mary's Hospital in that City on August 17, 1934. He was in his sixty-seventh year.

Dr. Lovett was born in Montreal on July 6, 1868,

and was educated at local Catholic schools, and later studied at St. Joseph's College, Memramcook, N.B. He graduated with his B.A. degree. He studied medicine at both McGill University and Laval University. He first started practising in old Griffintown. Later he moved to St. Denis boulevard where he enjoyed a large clientèle.

Besides his widow, formerly Annie Clare McGarty, he is survived by four daughters, the Misses Margaret, Agnes and Josephine Lovett and Mrs. Thomas Levins, Jr.; one sister, Mrs. M. E. Cummins, of Bath, N.B.; and one brother, Patrick Lovett.

Dr. John Alexander MacArthur, one of the grand old medical men of Winnipeg, died on August 26, 1934, at the advanced age of 86 years, fifty of which were spent in Winnipeg. He was born in Lobo township in the County of Middlesex, Ontario, and graduated in medicine in 1875 from McGill University. His first field of practice was in Clinton, Iowa, but, hearing of the development of the Canadian West, and being anxious to live under the British flag, he came to Winnipeg in 1884 and identified himself actively with the life of the community in medical, social, sporting, political and religious circles. He was for many years a member of the Faculty of Manitoba Medical College and Professor of Medical Jurisprudence, and, in later years, lectured on mental diseases and diseases of children. He was consulting physician to the Winnipeg General Hospital and to St. Boniface Hospital, president of the Winnipeg Medico-Chirurgical, and vice-president of the Canadian Medical Association. For a number of years he was Winnipeg surgeon of the Northern Pacific Railway and in 1908 he was named as a delegate to the World's Medical Congress in France which he attended. He was also member of the British Association for the Advancement of Science, and also the American Public Health Association.

In political circles he was a life-time Liberal. He served as president of the Winnipeg Liberal Association, and in 1903 and again in 1907 contested unsuccessfully the Centre Winnipeg seat of the Manitoba Legislature. Among the temperance people of the province he made strong friends by his life-long advocacy of their cause. He was president of the Dominion Alliance for Manitoba. A worthy son of the Scot clan he was closely identified with the Scottish organizations of the province. He was president of the St. Andrew's Society and Clan Stewart.

He was married in 1872 to Miss Lucile C. Casey, daughter of Col. Casey, a near relative of President Jefferson Davis of the U.S. Confederacy. Mrs. MacArthur was a distinguished artist and her pictures were hung in the Paris Salon and the World's Fair at Chicago. She died at sea in 1902. At the time of his death Dr. MacArthur was physician to the Provincial Gaol, a position which he held since 1916. He was one of the pioneer medical motorists of the province. A host of friends will remember him as a beloved physician and a kindly gentleman with manners of the old school and a disposition that remained sunny in spite of adversity.

ROSS MITCHELL

Dr. Donald McGregor MacKay, of Vancouver, one of the best loved of our profession, died in his sleep, on August 29th, at the age of sixty-five. A native of Nova Scotia, he had studied at Pietou Academy and Dalhousie University. He took his M.D. at Jefferson, in 1896, and for a time practised in Montana. In 1903 he came to Vancouver, so that he was one of the oldest active practitioners in the city. A keen wit, an enthusiastic golfer, and a sound diagnostician, known to his intimates as "Danny", he will long be missed, wherever an interesting case or a good anecdote is being discussed. He is survived by his wife, one daughter, and two sons.

Dr. Mary Muriel Currie MacLennan, Assistant in Anæsthesia at the University of Western Ontario, died in London, Ont., on August 22, 1934, after an illness of several months. She had practised medicine in that city for about three years.

Dr. MacLennan was born in 1892, and was a graduate of McGill University (1927). For two years she was an interne at the Victoria Hospital here and later established her own practice. She was a daughter of Rev. Dr. George MacLennan, of Montreal.

Surviving, besides her father, is one sister, Dr. Helen MacLennan, a graduate, last year, of the University of Western Ontario, and an interne at the Victoria Hospital.

Provincial Secretary, the Hon. G. M. Weir, has expressed the opinion that health insurance will prove more economical than our present haphazard methods of handling sickness.

The Greater Vancouver Health League announces continued gains in the study and prevention of tuberculosis in and about Vancouver. During 1933 there were 1,367 known cases of the disease and 200 deaths in the city. New cases reported during 1933 reached a total of 778, which is to say, two new cases a day. As is usual in fights of this kind, the crying need is for more hospital beds.

The ranks of the profession in Vancouver have suffered sadly during the past month, no less than four physicians having died. Drs. A. P. Procter, T. L. Butters, D. M. Mackay and E. W. Connolly have passed on.

C. H. BASTIN

News Items

Alberta

A special informal meeting of the Executive Committee of the Alberta Medical Association, the new members-elect of the 1935 Executive Committee, as well as the Council of the College of Physicians and Surgeons, was called for September 15th, to meet with Dr. T. C. Routley, who was making a tour of the West. The idea of the meeting was to confer with the General Secretary on how the other provinces are solving their difficulties due to the present depression.

It has been announced in the press that the Hon. G. Hoadley is calling a special meeting in Edmonton shortly of representatives of all organized bodies especially interested in health insurance. The delegates are to meet in the Medical Building of the University of Alberta, in conference with the Minister of Health, on health insurance. It does not appear to be intended as a meeting to actually do anything other than educational, as representatives of all the rural municipalities, apparently, are not being called.

The Government is sending to the north country a special Health Clinic to remove tonsils and make health examinations, similar to what was done some years ago. The announcement states that the clinic will go only to those places where qualified physicians are not practising.

Several municipalities are making arrangements with local physicians to inoculate and vaccinate their children at a special rate, as agreed upon with the Council of the College of Physicians and Surgeons some years ago. This is to be done on certain days, in groups, probably adjacent schools cooperating and bringing the children to a central point.

It would seem that something should be done to make motorists provide a fund from which first aid and hospitalization expenses could be met. At the present time the injured are usually without funds and hospital and physician do the work for nothing.

G. E. LEARMONTH

British Columbia

It is reported that in the recent questionnaire on health insurance, submitted by the Provincial Government, 80 per cent of the profession expressed themselves as in favour of the proposal. It is certain that legislation on the matter will be introduced shortly. Fifty thousand hospital cases have been studied from an actuarial standpoint in connection with the project, and these investigations are being continued. The

Manitoba

A meeting of the medical profession of Winnipeg was held in the Medical College on August 29th. Dr. E. S. Moorhead, Chairman of the Committee on Sociology of the Manitoba Medical Association, presented a recommendation from the committee that the reduction in the scale of fees for medical care of patients on unemployment relief proposed in a letter from Alderman Andrews, Chairman of the civic committee on relief, be approved. Dr. Moorhead pointed out that the present arrangement between the City Council and the doctors of Winnipeg, whereby the latter were paid for medical services to those on relief had been in force since February 22nd. He stated that the City Council had believed that after the scheme had been put in operation that the Provincial and Federal Governments would assist. In that expectation the Council had been disappointed, and, to add to the burden, the Federal Government had recently announced its decision to reduce the assistance to the City of Winnipeg by 13½ per cent. The proposed reduction was a cut of 33 1/3 per cent on hospital visits, that is 50c. in place of 75c. heretofore paid, and of 50 per cent for major surgical operations, so that in future \$25.00 would be paid by the city for a major operation in place of \$50.00. Dr. Moorhead pointed out that in the five months during which the scheme had been in operation 42 per cent of the sum paid to the doctors had been for surgical operations. After some discussion the meeting agreed to accept the proposal of the committee on unemployment relief, with the proviso that if the Provincial or Federal Governments, or both, should give assistance to the city the former schedule of fees would prevail.

From August 13th the hospitals and clinics of Greater Winnipeg which have outpatient departments have agreed that no patient will be admitted for consultation or treatment in the outpatient department except on the production of a letter from a private practitioner. It is understood that this rule is not to be enforced so rigidly as to shut out actual cases of emergency. Undoubtedly in times past there has been abuse of the outpatient departments and the present arrangement should go far to remedy that abuse.

The following appointments have been made to the Honorary Staff of the Winnipeg General Hospital: To be Assistants in Medicine: Drs. G. C. Stevens, F. A. L. Mathewson and C. H. A. Walton. To be Assistant in Obstetrics, Dr. Elinor F. E. Black. To be Assistant in Gynæcology, Dr. Blake Watson.

Members of the Honorary Attending Staff of the Winnipeg General Hospital gave a dinner at the Mani-

toba Club on August 30th to Dr. B. J. Brandson on the occasion of his retirement as Professor of Surgery of the University of Manitoba. ROSS MITCHELL

New Brunswick

Preliminary to a re-organization of staff in the Provincial Hospital, the New Brunswick Government was fortunate enough to obtain the services of Dr. E. A. Clark, Inspector of Ontario Hospitals, to make a report on the plant and management of the New Brunswick Institution. Arrangements for Dr. Clark's services were made through the efforts of Hon. Dr. Taylor, Provincial Minister of Health, and Dr. Warwick, Chief Medical Officer for New Brunswick.

Dr. Ernest C. Menzies, until lately Assistant Superintendent at the Verdun Hospital for the insane, has been appointed Superintendent of the Provincial Hospital at Fairville, N.B. Dr. Menzies was born in Kings County, educated at McGill University, and comes to his new post with the highest opinions from his associates. He succeeds Dr. J. V. Anglin, retired.

On August 18th, Hon. Dr. Murray MacLaren, C.M.G., V.D., Minister of Pensions and National Health, was host at the Riverside Country Club to his fellow members of the Saint John Medical Society, the occasion being the 50th anniversary of the doctor's graduation from medical school at the University of Edinburgh. The dinner was attended by practically every member of the local Society. Dr. J. P. McInerney, President of the Saint John Medical Society was requested by Dr. MacLaren to preside. Short intimate after-dinner addresses were made by Drs. MacLaren, Walter W. White, and George Addy. Dr. Addy presented Dr. MacLaren with a silver tray, suitably inscribed, as a gift from the Saint John Medical Society. During the course of the dinner Dr. MacLaren presented to the local Society the manuscript of Dr. Wm. Bayard's presidential address to the Canadian Medical Association. This address had been in the hands of Dr. F. N. G. Starr, who at his own expense had had the manuscript suitably bound for presentation. The manuscript will now find a resting place in the archives of the New Brunswick Museum.

A. S. KIRKLAND

Nova Scotia

A newspaper report announces the appointment of Dr. J. L. Churchill, of Halifax, to the post of Superintendent of the Nova Scotia Hospital. He is to succeed Dr. F. E. Lawlor who is retiring on account of ill health. Dr. Churchill, a former Chairman of the Halifax City Health Board, will spend the next four months in New York in a survey of hospital methods before assuming his duties here.

Dr. Gordon McCurdy takes up his duties as Lecturer in Bacteriology in the Medical School of Dalhousie University at the beginning of this term. He spent the past year in post-graduate work in the University of Glasgow, working under the direction of Professor Muir.

Dr. H. G. Grant, Dean of the Faculty of Medicine and Professor of Public Health in Dalhousie University, gave a discourse on "Tularæmia" to the group of physicians and surgeons attending the Refresher Course recently. He stated that the disease has been noted in human beings in Nova Scotia. The agglutination test in these cases was typical of tularæmia.

The Refresher Course sponsored by Dalhousie University was held from September 3rd to 7th inclusive. The attendance reached a total of ninety-four. All clinics and lectures were well attended. The visiting lecturers were Dr. L. J. Austin, Professor of Surgery at Queen's University and Dr. R. W. Simpson, physician to the Hospital for Sick Children, Toronto.

The death of Dr. E. O. Hallett in his seventy-fourth year occurred recently at Weymouth. He had been ill for a long time. He graduated from McGill University forty-five years ago. Before moving to Weymouth, some forty years ago, Dr. Hallett had engaged in practice at Arichat and Descousse.

N. B. DREYER

Ontario

The Honourable Dr. J. A. Faulkner, Minister of Health for the Province of Ontario, announces that in future all appointments to the Ontario Hospital Service, which includes the large mental hospitals of the province, will be by examination. The asylum service will no longer be available for old and worn-out party workers.

Tenders have been accepted for the construction of a tuberculosis sanatorium at Fort William at a cost of \$150,000. The first sod was turned on August 28th by Dr. Walter P. Hogarth, Chairman of the Board of Directors. The institution, when completed, will probably represent a total outlay of one-quarter of a million dollars.

Dr. A. B. Macallum, for many years Dean of the Faculty of Medicine of the University of Western Ontario, has tendered his resignation. It has been accepted and Dr. F. J. H. Campbell, Associate Professor of Medicine, has been appointed Acting-Dean.

The Ontario Hospital at Orillia is to be enlarged to accommodate approximately 1,000 additional patients. This will probably mean an expenditure of over two million dollars. These extra beds will take care of the 900 children on the waiting list. The present population in this hospital is 1,834.

The Honourable J. A. Faulkner, Minister of Health for the province, has recently sent a circular to the hospitals with respect to the admittance and care of welfare patients. It was advised that patients be examined by a committee of three doctors within twenty-four hours after their arrival at the hospital, and that regular examinations take place every week thereafter. It is hoped that, by this measure, no patients will remain in hospital a day longer than is necessary.

The exhibit relating to the history of medicine in the Province of Ontario has attracted a large number of visitors to the Academy of Medicine, Queen's Park, Toronto, and has created much newspaper comment. This exhibit represents a part of the contribution of the Academy of Medicine, Toronto, towards the celebration of the Centennial of the Corporation of the City of Toronto.

Dr. Septimus Thompson has been elected President of the Alumni Association of the Medical Faculty of the University of Western Ontario.

The monthly meeting of the Northumberland and Durham Medical Society on July 19th at Campbellford was addressed by Dr. H. A. Boyce, of Kingston. The subject discussed was the heart, and a number of clinical cases were used for demonstration.

The next meeting of this Society was held in Cobourg on September 6th, the speaker being Dr. H. W. Johnston, of Toronto, who gave an address on "Acute pelvic pain".

The next meeting of the Society will be in connection with the annual District Meeting at Peterborough on October 10th.

J. H. ELLIOTT

Quebec

At the last session of the Legislature, several amendments were enacted to the Quebec Public Health Act.

Two new articles, Nos. 41a and 41b make it compulsory for owners or builders of camps to serve as dwellings for the workmen in lumber camps, mines or road construction, to build according to standard plans supplied by the Director of the Provincial Bureau of Health and vest in him the right of control over the sanitary conditions of such camps. Contraventions are punishable with a fine of \$50.00 per day.

In Article 56, two new paragraphs concern cross-sections between public and private water supplies. New cross-sections are prohibited; the plans and specifications of those already in existence are to be submitted to the Director of the Bureau who has the power to modify or prohibit them.

To article 61 is added a paragraph vesting in the Public Utilities Commission the right of control over waterworks systems.

In the section concerning Foods and Beverages, two new articles, Nos. 71d and 71e, concern germ carriers: workers in pasteurization plants or in butter or cheese manufactures must undergo a medical examination as prescribed by the Director of the Bureau; germ carriers when found are excluded from all handling of milk, cream, cheese and other milk products, as well as from the handling of all foods destined to human consumption.

Article 76a assimilates a germ carrier to a patient as regards notification, isolation, disinfection, etc.

Article 80a vests in the Lieutenant-Governor in Council the right to render compulsory anti-typhoid or anti-diphtheria vaccination under certain conditions.

The use of the methods prescribed by the Provincial Health By-laws is made compulsory by Article 87a for microbial disinfection, the destruction of rats and of insects.

The Health Units Act, as it existed in Chap. 186a of the Quebec Revised Statutes 1925 is replaced by a new chapter also numbered 186a.

Art. 2—The Health Units already existing become permanent organizations.

Art. 3—The establishment of new Health Units is subject to an Order in Council.

Art. 4—Municipal Corporations in counties where there is a Health Unit must pay an annual contribution of one and a half cent per one hundred dollars of the municipal valuation of their territory.

Art. 5—Independent municipalities in a Health Unit must pay the same contribution, but those that have a population of 4,000 or over must pay two cents per \$100.00.

Art. 6—When such contributions are insufficient, the budget of the Unit may be completed by the Provincial Treasury.

Art. 7—Cities and towns of a population of 20,000 or over, where there is a sufficient Public Health organization, are excepted from the operation of the preceding Articles.

Art. 8—The fiscal year of the Health Units is the same as for the Province.

Art. 9—Health Units are the municipal sanitary authorities for the notification of contagious diseases.

Art. 10—The Medical Officer of the Health Unit, or, in his default, the Sanitary Inspector, is the Executive officer of the municipal sanitary authority of any municipality in its territory.

Art. 11—Contributions from sources other than those above mentioned may be accepted.

Art. 12—Health Units are under the direction and control of the Director of the Provincial Bureau of Health.

Art. 13—In counties under a Health Unit, the Medical Officer possesses all the powers of the Medical Inspectors of the Bureau and of the Municipal sanitary authorities.

Art. 14—The Health Unit Medical officers are appointed by the Lieutenant-Governor in Council.

Dr. K. A. Jarry, of Montreal, was named president of the 14th Congress of French-speaking Physicians of North America to be held in Montreal in 1936. Dr. Jarry is professor of physiotherapy at the University of Montreal, and director of the Bruchesi Institute. Dr. Amedée Granger, a prominent Louisiana surgeon, and professor at Tulane University, was named vice-president.

Election of officers of the European Association of French-speaking physicians took place also, Prof. Marcel L'Abbé being named president and Prof. J. Harvier, secretary. Prof. L'Abbé is well-known in France. The visiting European delegates decided to hold the next congress of the European Association in Paris.

The following have been appointed to the Staff of the new Jewish General Hospital in Montreal.

Medicine.—Joseph Kaufman, M.D., C.M., F.A.C.P., F.R.C.P.(C.), Consulting Physician; Physician to the Royal Victoria Hospital; Assistant Professor of Medicine at McGill University.

Surgery.—Edward Archibald, B.A., M.D., F.A.C.S., Hon. F.R.C.S.(Eng.), Consulting Surgeon; Surgeon-in-Chief, Royal Victoria Hospital; Professor of Surgery at McGill University.

Gynecology and Obstetrics.—James Robert Goodall, O.B.E., B.A., M.D., C.M., D.Sc., B.C.O.G., F.A.C.S., Professor of Clinical Gynecology and Obstetrics, McGill University, Montreal; Gynecologist and Obstetrician, Royal Victoria Montreal Maternity Hospital; Gynecologist and Obstetrician to the Homeopathic Hospital, Montreal; Consulting Gynecologist, Saranac General Hospital, N.Y.; Consulting Gynecologist, Alie Hale General Hospital, Malone, N.Y.; Fellow American Gynecological Society.

Pædiatrics.—Alton Goldbloom, B.A., M.D., F.R.C.P.(C.), F.A.P.S.; Lecturer in Pædiatrics, McGill University; Physician to the Children's Memorial Hospital and Foundling Hospital, Montreal; Consultant, Champlain Valley Hospital.

Oto-Laryngology.—A. O. Freedman, B.A., M.D., Chief of the Oto-laryngological Department of the Women's General Hospital; Assistant in the Ear, Nose and Throat Department, Montreal General Hospital; Chief of the Ear, Nose and Throat Department at the Herzl Dispensary; Oto-laryngologist at the Mount Sinai Sanatorium, and Chairman of its Medical Board.

Ophthalmology.—J. Rosenbaum, M.D., M.C., F.A.C.S., Assistant Ophthalmologist, Royal Victoria Hospital and Herzl Dispensary; on the Teaching Staff of the McGill University Ophthalmic Department.

United States

The first International Assembly of the Inter-State Post-Graduate Medical Association of North America to be held east of the Alleghenies is to take place in the public auditorium of Philadelphia, Penn., on November 5, 6, 7, 8 and 9, 1934, with pre-assembly clinics on November 3rd and post-assembly clinics on November 10th in the Philadelphia hospitals. The public auditorium is located in the university area and across the street from the Philadelphia General Hospital, thus



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The aim of the program committee, with Dr. George W. Crile, as chairman, is to provide for the medical profession of North America, an intensive post-graduate course covering the various branches of medical science. The program has been carefully arranged to meet the demands of the general practitioner as well as the specialist. Extreme care has been given in the selection of the contributors and the subjects of their contributions.

The Philadelphia County Medical Society will be host to the Assembly and has arranged an excellent list of committees that will function throughout the Assembly. A most hearty invitation is extended to all members of the profession who are in good standing in their State or Provincial Societies, to be present and enjoy the hospitality of Philadelphia, "The City of Brotherly Love". A list of distinguished teachers and clinicians who are taking part on the program will be found on page xxxv of the advertising section of this *Journal* (Sept., 1934). Among the participants we notice the names of the following Canadians, Drs. Campbell Howard, Montreal, Perry G. Goldsmith and Roscoe Graham, both of Toronto.

Special reduced railroad rates will be in effect on all lines.

The Cook County Graduate School of Medicine will offer on October 22nd, a two-weeks' intensive course in internal medicine; a two-weeks' intensive course in ear, nose and throat, and a ten-days' intensive course in fractures and traumatic surgery. These courses will be given provided the required number of doctors are registered for the work; also, they will be limited as to the number permitted to take the work. The clinical work will be given in the Cook County Hospital and the didactic work in the school building.

Professor d'Hérelle has resigned his chair at Yale University for the directorship of the Institute of Infectious Diseases at Tiflis, where he will continue his studies on the bacteriophage.

Book Reviews

Vital Cardiology: A New Outlook on the Prevention of Heart Failure. Bruce Williamson, M.D., M.R.C.P.(Lond.), Physician, Royal Northern Hospital, London, etc. 344 pages. Price \$4.95. E. & S. Livingstone, Edinburgh; Macmillan Co., Toronto, 1934.

This volume is a real contribution to the subject of cardiology. It is full of practical points based on physiology and common sense, and is written in a most delightful style, carrying the reader rapidly through its pages and leaving him with the desire to read the contents again. The author clearly shows how the heart may be directed along economic lines by considering two primary factors, namely, rate and force, keeping the underlying principle of the specificity or fixation of function in cells in mind. Following a brief consideration of the development of the heart, the three components in the cardiac cycle are ably discussed. These are the genetic system, the cardiac innervation and the myocardium. A plea is made for a wider recognition of the limits of electrocardiography. Part 2 of the book is a study of rate and force. It is pointed out that the true significance of abnormal rates lies in the degree of interference which they produce in the force of the myocardium.

Two most practical tests are thoroughly discussed, namely, the apnoea test and the basal-sleep rate. Following a consideration of the myocardial potential, a chapter is devoted to the assessment of the myocardial force, the importance of making a study of the individual being stressed. In considering the significance of valvular defects, attention is aptly drawn to the normal physiology of the heart and how alterations in such may affect the rate and force of the heart. Murmurs are only significant when affecting these fundamental factors. Part 3 deals with the cardiac symptoms of palpitation, dyspnoea, cyanosis, oedema, præcordial pain and angina pectoris and coronary occlusion. The final part of the book is on treatment.

The author is to be commended on his able presentation of his subject, and this book could be read with profit by both the general practitioner and specialist.

The Anæmias. Janet M. Vaughan, D.M.(Oxon.), M.R.C.P.(Lond.); Beit Memorial Fellow, Bernhard Baron Institute of Pathology. 284 pages, illustrated. Price \$4.00. Oxford University Press, London; McAinsh & Co., Toronto, 1934.

This volume is a brief but concise review of the clinical and hæmatological features of the more common types of anæmia. In the first chapter the author deals with normal erythropoiesis. There follows a lengthy classification of anæmias. The third to the fifth chapters deal with what have been called "Deficiency Dyshæmopoietic Anæmias". These anæmias are divided into groups caused by (1) lack of iron; (2) the pernicious anæmia factor; (3) vitamin C, and (4) thyroxin. Subsequent chapters deal with the anæmias due to hæmorrhage, toxins, hæmolytic agents, etc. The book is really a complete review of recent literature. The anatomy of erythropoiesis and the pathological anatomy of many of the anæmias is from the pen of Prof. H. M. Turnbull.

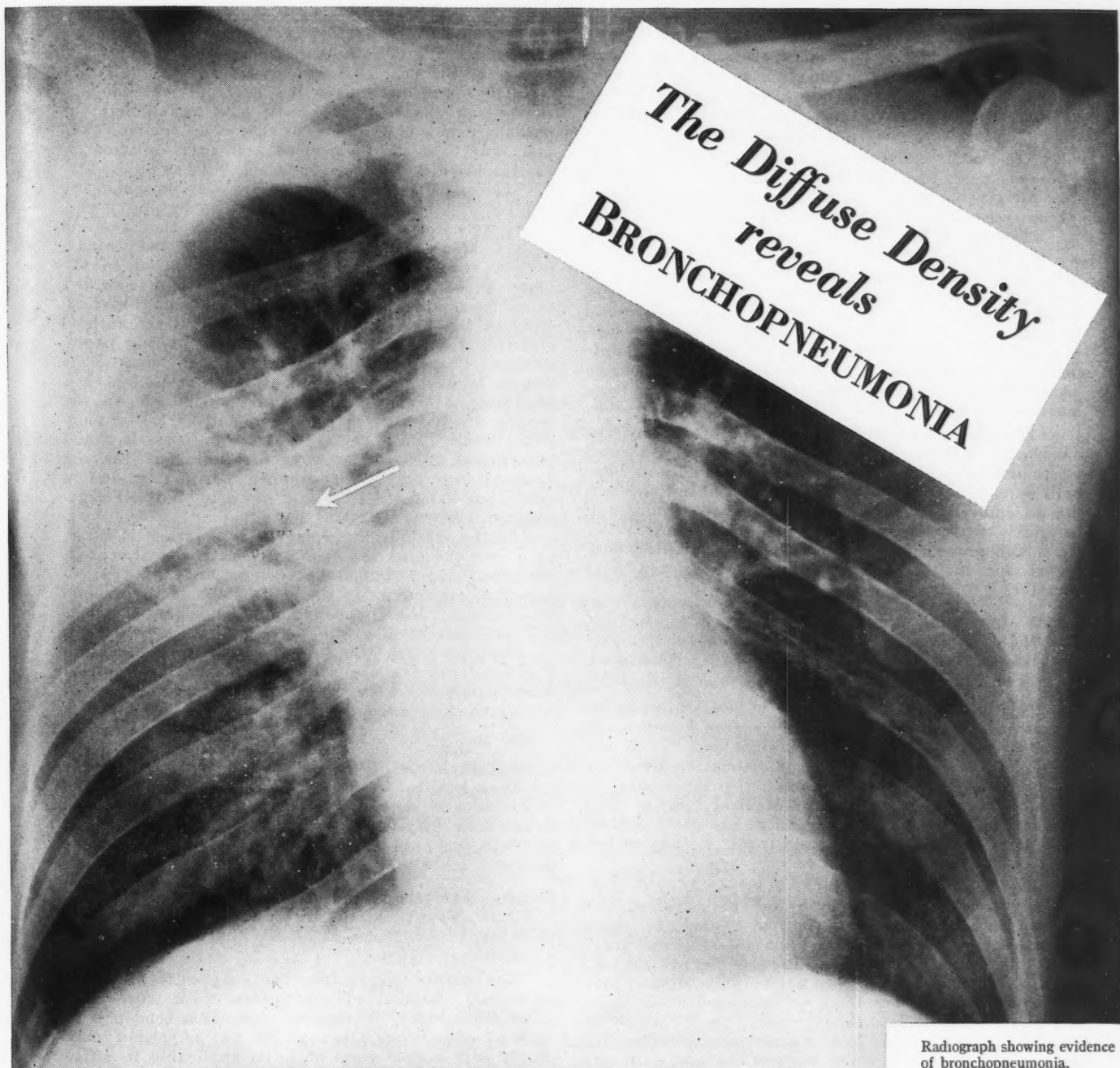
Medical and Orthopædic Management of Chronic Arthritis. Ralph Pemberton, M.S., M.D., F.A.C.P., Prof. of Medicine, University of Pennsylvania, and Robert B. Osgood, A. B., M.D., F.A.C.S., John Ball, and Buckminster Brown, Prof. Emeritus of Orthopædic Surgery, Harvard Medical School. 403 pages, illustrated. Price \$6.00. Macmillan Co., New York and Toronto, 1934.

This volume is the fruit of many years of intensive study of a disease entity that has been recognized since history began. It may well be, as the authors suggest, the most ancient of all known diseases. It is common to every race and climate, affects both men and women, and is also found among the lower animals. To study its literature would be an occupation for a lifetime.

The authors have adopted the simplest of classifications, using the terms "atrophic arthritis" and "hypertrophic arthritis" in much the same sense as Garrod uses the terms "rheumatoid arthritis" and "osteo-arthritis". A condensed but comprehensive account is given of the pathology of the disease, and the physiology of the whole organism, as it applies to the manifestations in the joints, is reviewed in such a way that the reader is informed of the important points and referred to more detailed studies in other publications. Everywhere throughout the book credit is given to other workers who have made significant additions to our knowledge of chronic arthritis.

In discussing etiology the writers give full weight to focal infection as a chief factor, but feel that its emphasis closed the book to medical men generally and discouraged search for other important factors which would have sooner emerged and modified the treatment of what the authors believe to be "a preventable and curable disease".

Among these other factors which are grouped as "physiological imbalance" are impairment of local



Radiograph showing evidence of bronchopneumonia.

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circulation, derangement of metabolism through gastro-intestinal derangement in consequence of visceroptosis, and the trauma of strains due to poor postural habits. These, and other conditions, are carefully evaluated and the rôles they play are logically estimated.

Treatment is based upon etiology and physical therapy; rest, exercise, drugs, diets, and elimination are all given a place in the rational management of these cases. The eradication of possible or actual foci of infection is but one of several means to the end of bringing relief or cure. "If the mere presence of pathogenic organisms focally imprisoned or free in the blood stream did, under ordinary circumstances, produce chronic disease the sick of the world would greatly outnumber the well" (page 187). A very effective method of bringing home to the reader the points made by the authors is the free use of analogies from other diseases against which we are making more effective efforts.

The section on orthopædics is prefaced by the statement that the work is written for to-day as well as to-morrow. When the light which the authors hope will spread over the world becomes visible there will be no end-results of chronic arthritis to require any surgical treatment. The present demand for relief from and prevention of deformities is adequately provided for in the procedures detailed in the final chapter.

Acute Intestinal Obstruction. Monroe A. McIver, M.D., Surgeon-in-Chief, Mary Imogene Bassett Hospital, Cooperstown, N.Y. 430 pages, illustrated. Price \$7.50. Paul B. Hoeber, Inc., New York, 1934.

This monograph has appeared in serial form in the *American Journal of Surgery*. Since then however new material and references have been added. It is the result of careful study and generalization of work compiled by the author while at the Massachusetts General Hospital and Harvard Medical School. The monograph includes both the clinical and physiological aspects of acute obstruction, and requires study rather than casual reading.

The book is divided into three parts. The first deals with the general picture of the disease; the second with diagnosis and treatment; and the third discusses the cause of death from intestinal obstruction. The author considers this complicated subject from all angles and discusses not only his clinical and laboratory findings but those of many contributors on the subject in the last thirty years. Each chapter is compiled with a resumé and an extensive bibliography. In the second part, definite suggestions are made regarding treatment and management, based on physiological indications. Discussion as to the cause of death in uncomplicated obstruction seems logical, and while the author believes that toxæmia may play a part, yet he believes that the major rôle is that of dehydration of the patient.

The work is recommended for study by all those who are interested in the abdominal surgery and also it would be, with its many references, an adjunct to those doing research in this field.

Diseases of Women. By ten teachers under the direction of Comyns Berkeley, M.A., M.D., M.C., F.R.C.P., F.R.C.S., M.M.S.A., F.C.O.G. Fifth edition, 568 pages, illustrated. Price \$5.50. Ed. Arnold, London; Macmillan Co., Toronto, 1934.

This is almost the ideal text-book for students. Its size is right, it carries very little excess baggage, the type is clear, and the illustrations excellently synthesized to the needs of the text. The usual weakness of books written by several authors is that there are hiatuses as well as overlappings. This has been avoided here, and the book reads like the work of a

single author, a tribute unquestionably to the editorial ability of Sir Comyns Berkeley.

The work represents the current gynæcological thought of the British School; this means that the pathology is sound, and somewhat conservative. The new work on the endocrines and their relation to uterine bleeding has been included, but has apparently not had much effect in changing the nomenclature used in previous editions. It seems to be pretty generally accepted in gynæcological circles that the old classifications into Chronic Endometritis and Chronic Metritis are giving way to groupings based on the newer endocrine knowledge, which present a truer and more reasonable picture of benign uterine bleeding. Some of this has crept into this book, but the authors still felt it necessary to head a chapter of four pages, Chronic Corporeal Endometritis, which chapter is largely taken up with argument to prove that such a condition "forms only a small percentage of the lesions which result in prolonged and excessive menstrual loss." From the student's standpoint it would have made for a clearer understanding if the old nomenclature had been dropped completely and a newer one along the lines laid down by Wilfred Shaw adopted.

In the section on Salpingitis some space is taken up giving the pros and cons of operative treatment in the acute stage. Since the vast majority of gynæcologists never operate in the acute stage of the uncomplicated case this argument might have been left out, and more attention given to the palliative treatment. In this connection the book does not even mention that all acute cases of salpingitis which have settled down should have their cervixes and urethras treated to remove the gonococcal infection from those environs where it can do the most social damage.

The chapter on neurasthenia in women—a very important chapter in any gynæcological text-book—has been handled with considerable insight and thoroughness, and outstanding common-sense. It is one of the best chapters in the book. On the whole this text will probably prove of more value to the student than any other that has recently come on the market.

Urinary Analysis and Diagnosis. Louis Heitzmann, M.D., New York. Sixth revised edition, 385 pages, illustrated. Price \$5.00. William Wood & Co., Baltimore, 1934.

The author emphasizes the diagnostic value of urinalysis. Because of the success with more complicated laboratory procedures there is a tendency to overlook the information which the physician may obtain with simple tests of urine applicable in office practice. As in the previous editions of the book, the author draws attention particularly to the value of the microscope.

The chemical tests described are well known. A valuable contribution in this section of the book is the modification of the quantitative test for albumin in the urine with the Esbach reagent, which permits more complete and more rapid sedimentation of the coagulated material. The sediments of urine (crystalline and amorphous material, blood, pus, epithelium, casts, microorganisms and animal parasites, extraneous material, etc.) are very clearly illustrated. The descriptions of magnification which accompany each illustration are very useful, as they permit proper comparative studies. In a number of pages the interpretations of findings are clearly discussed. The author perhaps too greatly emphasizes the significance of epithelial cells. Though perhaps intensive study permits such fine differentiations as described, the reviewer is skeptical about the ease with which the greater number of cells can be correctly identified with respect to site of origin.

Exceptions could be taken to a number of statements throughout the book. For example, on page 65, in the brief reference to renal glycosuria, the

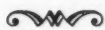
Acute and Generalized Staphylococcal Infections

Staphylococcus Antitoxin

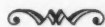
From various sources there has been an accumulation of evidence which suggests that much of the symptomatology of acute staphylococcal infections is attributable to liberation of staphylococcus exotoxin within the body. The serious nature of such infections would appear to be due in large measure to the highly pathogenic effects of staphylococcus exotoxin upon living cells and tissues. Consequently, the use of staphylococcus antitoxin has been advocated in the treatment of acute and of generalized infections where there is evidence that *Staphylococcus pyogenes* is the causal micro-organism. (See the issues of this Journal for June, July and August, 1934.)

As prepared by methods evolved in the Connaught Laboratories, Staphylococcus Antitoxin consists of refined and concentrated globulins from the blood-serum of horses which have been immunized against pooled toxoids and toxins of several selected strains of staphylococcus. Beneficial results have followed administration of this antitoxin in ACUTE CARBUNCLE and in CELLULITIS, OSTEOMYELITIS, MENINGITIS and SEPTICAEMIA, where staphylococcus has been the infecting agent.

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CANADA

statement that "in this condition there is *complete* (italics by the reviewer) lack of relation between the amount of sugar excreted and the amount of carbohydrates in the diet", is not in accord with the known facts about this condition.

Two short chapters at the end of the book are devoted to more recent and more complicated methods of diagnosis. One chapter deals with tests of functional efficiency of the kidneys, and, though the comments on findings are in accord with known facts, much has been left unsaid about the interpretation of such data. The chief value of this chapter is the drawing of attention to these tests; but, as they are well known, little more than this can be said. This applies equally to the final chapter—also brief—which deals with the hormone tests of pregnancy.

Textbook of Histology. Harvey Ernest Jordan, A.M., Ph.D., Professor of Histology and Embryology, University of Virginia. Sixth edition, 738 pages, illustrated. Price \$7.50. D. Appleton-Century Co., New York, 1934.

This well-known text now appears as an impressive-looking volume of 738 pages, well printed on heavy coated paper of a pleasant creamy tone, and bound sturdily in blue cloth. The subject-matter has been revised, and one notes modernizations in the sections dealing with the lymphoid organs, reproductive systems, reticulo-endothelium system, endocrine glands, striped muscle, nervous tissue and neuroglia. Not a few new figures have been added, including the handsome coloured one on mast-cells and Weed's classical diagrams of the sub-arachnoid space. Some have been replaced by better ones, but there is even yet room for improvement in a few instances. In a few places, too, illustrations could be inserted to advantage, as, for instance, a low power of the human pancreas, to replace the rather poor one of earlier issues, now deleted. In the section on technique one is glad to note such inclusions as Foot's method for reticulum, Sabin's procedure for the study of living blood cells, and Maximow's eosin-azure stain for hæmopoietic tissue. The Golgi apparatus (p. 9) should hardly be treated under the heading "mitochondria", but under its own caption. There has not been, perhaps, so much important change as the considerably bulkier volume would seem to promise. Seventeen pages are devoted to a list of illustrations which, for the ordinary reader, is of little or no value. On the whole, the presentation of this rapidly growing and very important science is reliably done, and the book is to be recommended to students in medicine.

An Introduction to Practical Bacteriology. T. J. Mackie, M.D., D.P.H., Professor of Bacteriology, University of Edinburgh, etc., and J. E. McCartney, M.D., D.Sc., Director of Research and Pathological Services, London County Council. fourth edition, 504 pages. Price \$4.15. E. & S. Livingstone, Edinburgh; Macmillan Co., Toronto, 1934.

In 1931 the third edition of this excellent text was rather fully reviewed in these columns. In this, the fourth edition, the subject matter has been divided into three sections for more convenient reference purposes. The volume has been increased in size by some eighty pages, owing to the addition of new knowledge and the rewriting and expansion of many paragraphs. Those chapters dealing with technique, Part II of this edition, which were highly commended in the previous review, still more deserve mention because of the introduction of fresh pointers of great practical value. The chapter on viruses has been considerably extended.

To the senior laboratory student and to those engaged in routine bacteriological and serological work this book can be highly recommended, particularly for the section on technique.

Recent Advances in Vaccine and Serum Therapy.

Alexander Fleming, F.R.C.S., Professor of Bacteriology, University of London, and G. F. Petrie, M.D., Bacteriologist-in-charge, Serum Department, Lister Institute, Elstree. 463 pages. Price 15s. net. J. & A. Churchill, London, 1934.

This is a survey of more than ordinary usefulness. Vaccine and serum therapy occupy a large place in everyday practice, and yet there is a technical atmosphere surrounding them which is apt to make their employment not so simple as that of drugs. It is true that even the most skilled in the preparation of vaccines admit to some degree of uncertainty of results, but there is still a large body of ascertained fact which may be consulted in this volume.

Part I deals with serum therapy and gives concise reviews of its use in those diseases in which definite results have been obtained. Chapters on serum treatment of snake-bite, scorpions and spiders, as well as on sera in veterinary practice, are included. Part II is on Vaccine Therapy, and, in addition to dealing with the commoner infections such as typhoid, dysentery, pneumonia, influenza, whooping cough, etc., has thorough and well digested reviews of the treatment of hay fever and asthma.

In all the book may be well recommended not only for its thorough review of a large field, but for its temperate estimate of what is being done in a most important branch of therapeutics.

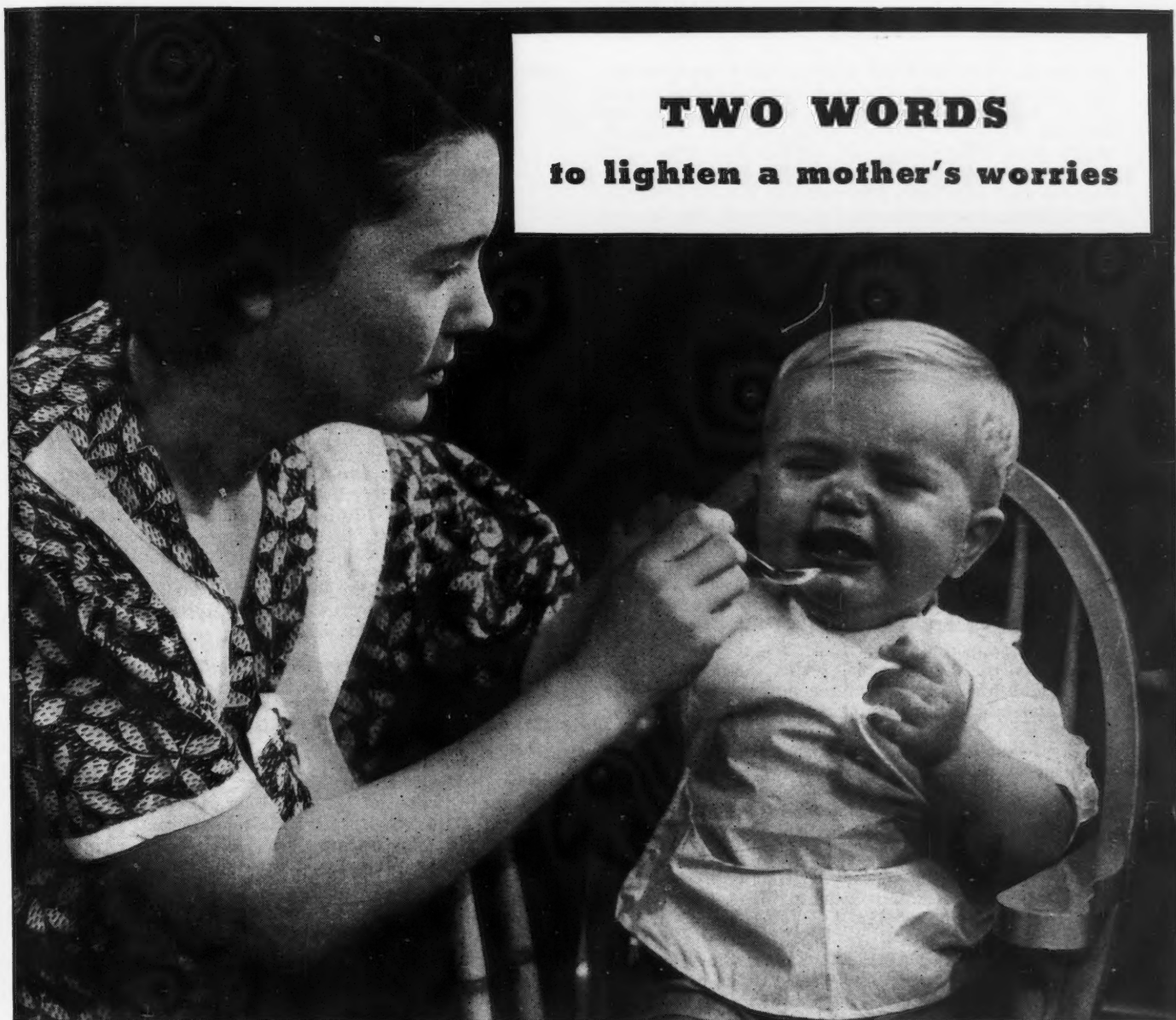
Modern Clinical Psychiatry. Arthur P. Noyes, M.D., Superintendent of State Hospital for Mental Diseases, Howard, R.I. 485 pages. Price \$5.25. W. B. Saunders, London and Philadelphia; Mc-Ainsh & Co., Toronto, 1934.

Stressing the psycho-biological concept in the study of modern psychiatry, and judiciously interpreting personality functions from this standpoint, the author of this publication has made the nature of human behaviour, normal and abnormal, psychologically understandable. The forces governing human behaviour and the mental mechanisms and motives controlling mental health are clearly described in the early chapters. Emphasized among the psychogenic factors in the production of mental disorders are the importance of intrapsychic conflicts and the symbolization that may show itself in the patient's behaviour, and the necessity for the psychiatrist to consider in his genetic analysis the interpretation of the patient's psycho-social and affective status. The various trends which the abnormal mental action may assume, irrespective of the cause, are described in a clear manner in a consideration of the symptoms of mental disease in general. The different types of major psychoses are discussed, with particular reference to the more common forms. The causative factors in the development of neuroses and psychoneuroses, being similar to those governing the major psychoses, and the symptoms intelligible only in psycho-biological terms, these conditions have been discussed under the "minor psychoses", a classification which probably will soon receive general adoption.

No doubt the original lectures as given to the students by the author have been, when put into the form of this volume, elaborated upon to a considerable degree. Sound psychological facts have governed opinions expressed, and the monograph is one which should be well received by graduates in medicine and related sciences.

Textbook of Pathology. William Boyd, M.D., M.R.C.P., F.R.C.P., Dipl. Psych., F.R.S.C., Professor of Pathology, University of Manitoba. Second edition, 1047 pages, illustrated. Price \$10.00. Lea & Febiger, Philadelphia, 1934.

There is little to add to previous reviews of this excellent book. It is only two years since the first



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edition was published but a great many changes have been made in it, not only in material but in arrangement. The clear, readable style, the well chosen "Additional Reading" lists of references, the extraordinarily good illustrations, are all familiar features of Dr. Boyd's book. The present edition keeps all these features and adds such new material as lead poisoning in children, pneumonia in the newborn, localization of infection, the St. Louis type of encephalitis, tobacco hypersensitiveness in Buerger's disease, etc. It has indeed been kept up to date.

The Diary of a West Country Physician 1684-1726.

Edited by Edmund Hobhouse, M.D. 155 pages. Price 5/- net. Simpkin Marshall Ltd., London, 1934.

Dr. Claver Morris (1659-1726/7) a graduate in Arts and Medicine of Oxford, practised at Salisbury and Wells. Not only a successful physician, he interested himself in the affairs of the community, held a number of public offices, was an extensive landowner, was an accomplished musician, and showed much talent in organizing musical entertainment. He loved social gatherings, yet found time to read classics, to work in his chemical laboratory, and amuse himself with mathematics.

He left behind him four large vellum-bound volumes of the ledger type, which contain detailed accounts of his receipts and expenses for forty-four years, and a diary with a complete daily record for over eight of the last years of his life. From these we learn what clothes he wore, what books he bought, what horses and carriages he had, what lands he bought and received. His manner of living and his entertainment, his amusements and journeys, are recorded with but little comment.

Dr. Edmund Hobhouse studied these records and at the time of his death had written eight chapters which form Part I of this Memoir. He writes of the daily life at Wells, of the food and liquor, of Dr. Morris' medical practice, the school life of his children, of his finance and prices of most things bought, of music and the musical clubs, and of his public and church activities. This forms an interesting sketch of the life of a physician and extensive landowner of the latter part of the seventeenth century. Part II gives extracts from the diary and from the account books.

It may be noted from the dates of Dr. Morris that he lived through five reigns, being born just before the proclamation of Charles II and dying a few weeks before the death of George I. One only wishes that Dr. Hobhouse had been able to write at greater length of the life at Wells, based on the material at his disposal in these old volumes.

BOOKS RECEIVED

Manual of Diseases of the Eye. Charles H. May, M.D., Formerly Director of the Eye Service, Bellevue Hospital, New York. Fourteenth edition revised, 496 pages, illustrated. Price \$4.00. William Wood, Baltimore, 1934.

Spinal Anæsthesia, Technic and Clinical Application. George R. Vehrs, M.D., Salem, Ore. 269 pages, illustrated. Price \$6.50. C. V. Mosby, St. Louis; McAinsh & Co., Toronto, 1934.

The Essentials of Physical Diagnosis. Robert W. Buck, M.D., Ass't. Professor of Preventive Medicine, Tufts College Medical School. 259 pages, illustrated. Price \$3.50. W. B. Saunders, London and Philadelphia; McAinsh & Co., Toronto, 1934.

Collected Papers of the Mayo Clinic and Mayo Foundation. Vol. 25. Edited by Mrs. Maud H. Mellish Wilson and Richard M. Hewitt, B.A., M.A., M.D. 1230 pages, illustrated. Price \$13.00. W. B. Saunders, London and Philadelphia; McAinsh & Co., Toronto, 1934.

International Clinics. Vol. 2, forty-fourth series. By various authors. 317 pages, illustrated. Price \$3.00. J. B. Lippincott, Philadelphia, London and Montreal, 1934.

Synopsis of Hygiene. E. W. Caryl Thomas, M.D., B.Sc., D.P.H., Barrister-at-Law, Medical Officer of Health, Dagenham. 283 pages. Price \$3.45. John Wright & Sons, Bristol; Macmillan Co., Toronto, 1934.

Food and Character. Louis Berman, M.D. 384 pages. Price \$2.50. Methuen & Co., London, 1934.

Mental Hygiene in the Community. Clara Bassett, Consultant in Psychiatric Social Work, Division on Community Clinics, National Committee for Mental Hygiene, Inc. 394 pages. Price \$4.20. Macmillan Co., New York and Toronto, 1934.

The Spastic Child. Marguerite K. Fischel. 97 pages, illustrated. Price \$1.75. C. V. Mosby, St. Louis; McAinsh & Co., Toronto, 1934.

Modern Advances in Diseases of the Throat. Arthur Miller, F.R.C.S., D.L.O., Surgeon for Diseases of Ear, Nose and Throat, French Hospital, London. 117 pages, illustrated. Price 10/6 net. H. K. Lewis, London, 1934.

Massage and Remedial Exercises. Noël M. Tidy, Sister-in-Charge of Massage Dept., Princess Mary's Royal Air Force Hospital, Halton. Second edition, 430 pages, illustrated. Price \$4.95. John Wright, Bristol; Macmillan Co., Toronto, 1934.

Diffuse Sclerosis. L. Bouman, M.D., Professor of Psychiatry and Neurology, Utrecht University. 160 pages, illustrated. Price \$4.95. John Wright & Sons, Bristol; Macmillan Co., Toronto, 1934.

Aids to Osteology. Philip Turner, B.Sc., M.B., M.S., F.R.C.S., Assistant Surgeon, Guy's Hospital. Second edition, 187 pages. Price \$1.35. Baillière, Tindall & Cox, London; Macmillan Co., Toronto, 1934.

International Clinics. Vol. 2, forty-fourth series. By various authors. 327 pages, illustrated. Price \$3.00. J. B. Lippincott, Philadelphia, London and Montreal, 1934.

Postures and Practices During Labour Among Primitive Peoples. Julius Jarcho, M.D., F.A.C.S., New York. 175 pages, illustrated. Price \$3.50. Paul B. Hoeber, New York, 1934.

The Constitution and its Reaction in Health. T. E. Hammond, F.R.C.S., Assistant Surgeon, Royal Infirmary, Cardiff. 160 pages. Price 7/6 net. H. K. Lewis, London, 1934.

Murrell's What to do in Cases of Poisoning. P. Hamill, M.D., D.Sc., F.R.C.P., Lecturer on Pharmacology and Therapeutics, St. Bartholomew's Hospital Medical College. Fourteenth edition, 208 pages. Price 5s. net. H. K. Lewis, London, 1934.

Synopsis of Medicine. Henry L. Tidy, M.A., M.D., B.Ch., F.R.C.P., Physician to St. Thomas's Hospital. Sixth edition, 1112 pages. Price \$6.25. John Wright & Sons, Bristol; Macmillan Co., Toronto, 1934.